



United States Department of Energy



Human Subjects Protection Resource Book



Preface

Purpose of This Resource Book

Although many federal organizations now have guidebooks, manuals, or handbooks in support of human subjects protection activities, the first major work developed with a broad perspective was the *Guidebook for Institutional Review Boards* in the early 1980s by Public Responsibility in Medicine and Research, a nonprofit organization. In 1992, the year following the formal adoption by 16 federal agencies of the Federal Policy for the Protection of Human Subjects (Common Rule), the U. S. Department of Energy (DOE) published the *Human Subjects Research Handbook (Protecting Human Research Subjects)*. In 1993, the Office for Protection from Research Risks, National Institutes of Health, issued *Protecting Human Research Subjects, Institutional Review Board Guidebook*, a new work. In 1995, a revised second edition of the DOE *Human Subjects Research Handbook (Protecting Human Research Subjects)* was published to address more current issues and concerns in the human research area.

By 2000, it was evident that accelerating changes in science, regulations, and practices would require that existing guidebooks and manuals be updated. Dr. Susan Rose, the DOE Human Subjects Research Program Manager, with the support of the National Science and Technology Council, proposed that major revisions to these guidebooks and manuals be undertaken to provide the human subjects research community with broader and more current information in the form of a resource manual. Dr. Rose was asked to take on the development of such a document as a federalwide project and formed a multiagency Resource Book Task Group to research and compile the information. Some participating departments or agencies made volunteers available to the task group for the research, compilation, and review efforts. Many others contributed their time and energy to the review process. (The participants in this project are identified in the *Acknowledgments* section of this manual.) This document is the result of several years of hard work by many dedicated individuals and the support of their institutions.

Thus, this resource book was a joint project of several agencies: DOE, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs. However, this manual does not represent the official views or policies of any of these or any other agencies. Rather, it is an attempt to synthesize the information currently available on the protection of human subjects in research, the continuing application of such information to new areas of endeavor, and the ever-changing rules, regulations, and guidance involved in the hope that it might provide useful information for investigators, Institutional Review Boards (IRBs), research organizations, research subjects, and others.

This book does not constitute regulations or formal federal agency guidance but rather has been prepared for the convenience and reference of the many audiences noted above. Regulations are cited when appropriate, as is federal guidance, but existing regulations and agency guidance may not always provide clarity or relevancy in the real world of research review and conduct. Therefore, where relevant citations from national advisory bodies have been used, readers are encouraged to explore the work of these advisory groups, as well as scholarly publications, to attain a greater appreciation of the complexity of the challenges at hand.

Some readers will find portions of the resource book too simplistic; and other readers will find these same portions to be an important primer, while the more advanced reader will employ this book as a useful reference. The book contains chapters that provide background information on the history and development of the federal regulations, chapters that discuss procedural and substantive issues regarding the review and conduct of human subjects research, and chapters that are specific to one type of research (e.g., genetics, biological samples) or research in specific populations (e.g., international settings, children, and workers).

The chapters in this book provide evidence that the issues with which IRBs, investigators, and research organizations must concern themselves are many and complex. We have tried to provide some expanded discussions of the regulations and beyond, but we do not presume to offer the definitive discussions of the many ways in which any reasonable reader might interpret the language of the regulations. An important goal of the resource book is to help facilitate understanding of the concepts involved, how they relate to human subjects research, and how one might go about applying those concepts. This resource book is not intended or designed to tell IRBs whether or not specific protocols should be approved (unless the regulations specifically prohibit the proposed activity or method). It does, however, describe the issues on which investigators, institutions, and IRBs should focus their attention. Furthermore, although the book is broad in scope, human subjects issues change. Thus, this document focuses on what are considered to be the most important issues and concerns to the human subjects community, rather than on attempting to be comprehensive or complete.

This resource manual frequently refers to the policies and guidance of all signatories to the Common Rule and often to the policies and guidance of the Office for Human Research Protections (OHRP) as the lead regulatory agency in this field. OHRP has been given permission by the Office of Management and Budget to negotiate Federalwide Assurances of Compliance, and, as such, many departments and agencies rely on OHRP's assurance system to implement their own systems of compliance oversight. However, departments or agencies might interpret the regulations differently or impose additional requirements for research they conduct or support. Readers are encouraged to find out whether their institutions or funding agencies have different or additional requirements. Although this book contains an Agency Chapter 27 for DOE, your agency may insert your human subjects chapter in its place. Each agency has the opportunity to add a Chapter 27 to this resource manual that will include agency-specific additional sections or references covering its pertinent research regulations, policies, and procedures.

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April 18, 1979

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Chapter 1

Roles and Responsibilities for Protecting Human Subjects

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 - C. The Principal Investigator (PI)
 - D. Other Members of the Research Team
 - E. The Institutional Review Board
 - F. The Institutional Review Board Administrator/ Director, Support Staff, and Institutional Review Board Office
 - G. The Research Sponsor
 - H. Research Subjects
 - I. Communities
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A. Introduction

This chapter summarizes the responsibilities for protecting human subjects that are expected of individuals and organizations involved in the conduct of human research. These responsibilities include following ethical principles, complying with federal regulations, and adhering to institutional policies.

The ethical conduct of human subjects research is an individual, organizational, and shared responsibility that includes all who contribute to the research endeavor—research team members, institutional officials, such as deans and department heads, Institutional Review Board (IRB) members and staff, research administrators, research sponsors, members of the community from which research subjects are drawn, and the research subjects themselves.

Protecting research subjects—an essential feature of the ethical conduct of human research—is also an individual, organizational, and shared responsibility. No single person can ensure that subjects are protected in every research project, or even in every component of any specific research project. Therefore, every person involved in the conduct of human research expects and depends upon each one of his/her colleagues to place the rights and welfare of subjects above other considerations.

The critical elements underlying the responsibilities related to human subjects protection derive from nationally and/or internationally accepted ethical principles, government regulations, and the policies of individual organizations conducting research. These elements are summarized in Table 1.1 and will be discussed in detail in later chapters.

Institutions involved in the conduct of research that is funded by the federal government have an explicit organizational responsibility to protect human subjects. Every organization, regardless of research funding source, conducting human research should have a program in place that provides the organizational structure, lines of communication, and other resources necessary to protect subjects. The *human research protection program* (HRPP) is a relatively new term adopted by at least one accreditation organization and described in detail in *Responsible Research: A Systems Approach to Protecting Research Participants* (IOM 2003). The term reflects growing awareness that institutions conducting research should have a system-wide program involving many units and functions to protect research subjects. There are many components of an effective HRPP, each with unique roles and responsibilities as well as shared and overlapping roles and responsibilities, including the institution conducting research, the Principal Investigator (PI),

**Human
Research
Protection
Program (HRPP)**

Table 1.1**Important Documents Relevant to Protecting Human Research Subjects****Ethical Standards and Codes**

- The *Nuremberg Code* (Nuremberg 1949)
- The *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 1964, revised most recently in 2002)
- The *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979)

Federal Government Regulations

- Federal Policy for the Protection of Human Subjects (or the Common Rule), codified for the Department of Health and Human Services (DHHS) at 45 CFR Part 46, Subpart A¹
- Regulations providing additional protections for pregnant women, fetuses, and neonates (for DHHS, at 45 CFR Part 46, Subpart B), prisoners (45 CFR Part 46, Subpart C), and children (45 CFR Part 46, Subpart D) involved in research
- Food and Drug Administration (FDA) Informed Consent Regulations (21 CFR Part 50)²
- FDA IRB regulations (21 CFR Part 56)³
- State laws and regulations

Local and Institutional Laws and Policies

- Administrative requirements (e.g., processing of grant applications, and contracts)
- Oversight requirements (e.g., protocol review and monitoring, biosafety and radiation safety)
- Professional qualification requirements (e.g., certification of IRB administrators, members, and staff)
- Organizational mission statements
- Organizational ethical standards

other members of the research team, the members of the IRB, IRB administrators and staff, research sponsors, and the community. The implication of having HRPPs is that the IRB cannot and should not be expected to fulfill all protection duties, even though it is the predominant unit addressed in the Federal Policy for the Protection of Human Subjects (or the Common Rule). The roles and responsibilities of each component unit of an HRPP are described below.

B. The Institution Conducting Research

Just as research programs need infrastructural support to survive and flourish, the oversight of human subjects protection also requires administrative resources to be viable and effective. This infrastructure and the activities it supports constitute the HRPP of the organization that conducts the research.

The review of proposed research by an IRB, described in detail in Chapter 11 of this manual, constitutes only one component of an effective HRPP. Organizational commit-

¹ Each codification of the Federal Policy for the Protection of Human Subjects by a department or agency is equivalent to 45 CFR 46.101-46.124 (Subpart A), DHHS codification. Each signatory to the Federal Policy, also called the Common Rule, codified the regulations separately; however, the individual sections of the regulations are identical to 45 CFR Part 46, Subpart A (except in their initial reference number), with the exception of the regulations of the Food and Drug Administration (FDA), in which the reference number and sometimes the language differ in some key areas (56 *Federal Register* 28002, June 18, 1991). Throughout this manual, the codification will be referred to as §____.XXX when citing the regulatory requirements of the Common Rule. Anyone looking at any version of the Common Rule, regardless of the agency that has signed on, will be able to recognize the codification using this format. The FDA requirements will also be cited. Throughout this manual, when both the Common Rule and FDA regulations are applicable, the Common Rule citation will appear first, followed by the FDA citation—for example, (§ .108(b); 21 CFR 56.108(c)). DHHS also adheres to Subparts B through D, which address special protections for vulnerable populations (discussed later in this manual). 45 CFR Part 46. Subparts A through D are available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm. Some departments and agencies also have incorporated some or all of the subparts into their policies.

² See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html.

³ See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html.

ment, accountable leadership, initial and continuing education programs, and compliance oversight activities are prerequisites for a successful HRPP.

The Common Rule delineates the responsibilities of “institutions” that are engaged in human subjects research conducted or supported by the federal departments and agencies that have adopted the policy. According to the

responsibilities of “institutions”

Common Rule, any such “public or private entity (including federal, state, or other agencies)” must “assure” the supporting or conducting department or agency in writing that it will comply with the regulations for protecting human subjects in research (§__103(a)).⁴

The regulations contemplate that this is accomplished through the use of a written assurance to the appropriate federal department or agency that the institution conducting the research will comply with the Common Rule—that is, it accepts its responsibility for protecting human subjects in a manner that is consistent with accepted ethical standards and specific regulatory requirements (see Chapter 5 for a lengthier discussion of the assurance process). Each legally

written assurance

separate institution must obtain its own assurance applicable to the research. Many institutions hold assurances

approved for federalwide use by the Office for Human Research Protections (OHRP), Department of Health and Human Services (DHHS). Until recently these included Federalwide Assurances (FWAs) and Multiple Project Assurances; currently the FWA is the only new assurance offered by OHRP (see Chapter 5). Such assurances cover all of the institution’s research involving human subjects that is conducted or supported by one of the federal departments or agencies that have adopted the Common Rule, provided the assurance is appropriate for the research in question (§__103(a)). The institution also must develop written operating procedures to ensure that these ethical standards and regulatory requirements are actually carried out in practice (§__103(b)).

The written procedures should delineate the institutional components and the institutional personnel that are charged with developing and implementing meaningful protections. Once delineated, the responsible components and personnel should be given the authority and resources to carry out their human subjects protection functions.

Ultimately, the institution’s highest officials and its governing body (i.e., board of directors or board of trustees) will be held accountable by the federal government and by the public for ensuring that the institution’s policies, procedures, and resources are effectively applied to the protection of human subjects.

Institutional Human Subjects Signatory Official

Each institution engaged in human subjects research conducted or supported by one of the federal departments or agencies that have adopted the Common Rule must designate an institutional official to execute the assurance of compliance. This individual must be authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the Common Rule (§__103(c)). It is the responsibility of this official to ensure that the institution develops, implements, and maintains an effective HRPP that complies with the requirements of the Common Rule. Specific responsibilities of the signatory, or responsible official, at a minimum must include:

responsibilities of the signatory, or responsible official

- ensuring the development and implementation of policies and procedures governing all of the institution’s research projects involving human subjects, research investigators, and research personnel who conduct such research, and IRBs (§__103(b)(4));
- designating one or more IRBs to be responsible for oversight of the institution’s human research (§__103(b)(2));
- ensuring that the institution’s IRBs are provided with sufficient meeting space (§__103(b)(2));
- ensuring that the institution’s IRBs receive sufficient resources, including technology and staff, to support their substantial review and record keeping responsibilities (§__103(b)(2));
- ensuring that institutional programs function in accordance with all federal, state, and local laws and regulations that govern human subjects protection in the conduct of research (§__101(f));
- ensuring the implementation of appropriate procedures for notifying institutional officials and researchers with oversight responsibility about 1) any unanticipated problems involving risks to subjects or others; 2) any serious or continuing noncompliance with the requirements of the Common Rule or the requirements or determinations of the IRB; and 3) any suspension or termination of IRB approval (§__103(b)(5); §56.113); and
- in coordination with appropriate institutional officials with oversight responsibility, ensuring prompt notification of FDA, any sponsoring federal department or agency, and the assurance granting office (e.g., OHRP) of such incidents in accordance with federal regulations (§__103(b)(5); 21 CFR 56.108(b)).

⁴ The Food and Drug Administration requires that any nonexempt clinical investigation should not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of regulations (21 CFR 56.103(a)).

Additional responsibilities of the signatory official may include:

- establishing effective lines of communication with the institution's highest officials and its governing body (i.e., board of directors or board of trustees) to ensure an understanding of their legal and ethical responsibilities for protecting human research subjects;
- promoting an institutional culture that values human subjects protection as a primary ethical value and personal responsibility;
- fostering understanding of, and compliance with, human subjects protection requirements throughout the institution;
- developing and implementing policies and procedures that govern all of the institution's research projects involving human subjects, research investigators, research personnel, and IRBs;
- ensuring that the institution's HRPP receives the resources needed to maintain effective systemic protections for human subjects;
- ensuring the establishment of initial and continuing education requirements relative to human subjects protection issues for research investigators, study coordinators, research staff, IRB members, and IRB staff;
- ensuring the provision of resources sufficient to maintain effective initial and continuing education programs relative to human subjects protection issues;
- ensuring that open channels of communication linking the institution's IRBs, IRB staff, research investigators, study coordinators, research staff, administrative staff, and any other relevant parties are maintained;
- monitoring the operation and administration of the institutional HRPP (including the institution's IRBs);
- arranging for internal and/or external, periodic, independent assessments or audits of the institution's HRPP in terms of regulatory compliance and overall effectiveness;
- providing the institution's board of directors, board of trustees, or other governing body with periodic reports that summarize the activities of the institution's HRPP;
- serving as a knowledgeable point of contact for federal regulatory agencies or assigning another individual to serve in his/her capacity.

The institutional official should have direct access to senior management, including the institution's chief executive officer and/or board of trustees/directors, if such access is needed to ensure the protection of human subjects.

C. The Principal Investigator

The lead investigator for a research project is referred to as the Principal Investigator (PI). As the individual directly responsible for the implementation of all aspects of the research, the PI bears direct personal responsibility for protecting every research subject enrolled in his/her research project. This responsibility starts with the design of the research protocol, which must meet several criteria stipulated by the Common Rule in order to be approved by the IRB (§___,111; 21 CFR 56.111). The research must be meritorious and the researcher should have the competence and resources to carry it out. Risks to subjects must be minimized by using procedures consistent with sound research design that do not unnecessarily expose a subject to risk and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purpose.

the PI bears direct personal responsibility for protecting every research subject

In accepting and exercising responsibility for all aspects of the research, the PI, at a minimum, should ensure the following:

- all members of the research team adhere to all accepted ethical principles as elucidated in the *Belmont Report* and comply with the findings, determinations, and requirements of the IRB;
- the informed consent process and the informed consent document are adequate, no matter which members of the research team actually conduct and document the consent process;
- the research has received prospective initial review and approval by an institutionally designated IRB;
- continuing IRB review and approval of the research is secured in a timely fashion;
- the research does not extend beyond the established IRB approval period;
- the research is conducted at all times in compliance with all applicable federal, state, and local regulatory requirements and in accordance with the IRB-approved protocol;
- the research is conducted at all times in accordance with the findings, determinations, and requirements of the IRB;
- any required data and safety monitoring plan is being implemented;
- all members of the research team are trained in and have a working knowledge of the following:
 - the institution's approved assurance of compliance;
 - relevant federal regulations, such as the Common Rule, FDA's informed consent and IRB

- regulations, and other relevant government regulations for protecting human subjects;
- the *Belmont Report* and the ethical principles it articulates;
- the research protocol, including all requirements, procedures, and enrollment criteria.
- all members of the research team receive appropriate supervision;
- no changes in the approved research are initiated without prior IRB approval, except when necessary to eliminate immediate hazards to subjects;
- the IRB and/or sponsor is notified promptly of the following:
 - any unanticipated problems involving risks to subjects or others;
 - any serious adverse events that are not described in the IRB-approved protocol and informed consent document;
 - any serious or continuing noncompliance with regulatory requirements or the determinations of the IRB;
 - any protocol deviations or any changes made to eliminate immediate hazards to subjects;
 - any proposed changes in previously approved research.
- detailed records are maintained and made available to responsible institutional officials regarding interactions that involve:
 - subjects,
 - the study sponsor,
 - the IRB,
 - relevant federal agencies.
- each potential subject understands the nature of the research;
- each subject (or the subject's legally authorized representative) receives a copy of the IRB-approved informed consent document, unless the consent requirement is appropriately waived by the IRB (§____.116(d); note that FDA regulations do not allow waiver of consent).

PIs should be encouraged to consult directly with the IRB chairperson or IRB professional staff, institutional human subjects signatory official, or institutional legal counsel about any matter or concern related to the protection of human research subjects.

D. Other Members of the Research Team

In addition to the PI, other investigators may share responsibility for the conduct of a research study. These investigators might be termed coinvestigators or sub-investigators. Regardless of their titles, all investigators and members of the research team must accept ethical and regulatory responsibility for the protection of human subjects. The PI is ultimately responsible for ensuring that these obligations are met, even when they are delegated.

Study coordinators (or research coordinators) frequently play a critical role in ensuring the quality and ethical conduct of a research project. Study coordinators are typically responsible for the day-to-day administration and conduct of the research project, with duties that may include interacting with subjects or potential subjects, delivering or facilitating research interventions, managing regulatory files and other required documentation, and supervising other members of the research team.

**study
coordinators**

Depending upon the nature of the research and the professional expertise of the individual, it may be the study coordinator who actually solicits, witnesses, or even conducts the informed consent process (including obtaining informed consent) from prospective subjects. Study coordinators regularly play a crucial role in explaining research procedures to subjects as well as risks, benefits, study purpose, and alternatives to participation before and after enrollment.

Study coordinators are often in the best position to observe the full range of research activities as they unfold in real-life settings. As a result of this unique vantage point, study coordinators are in a particularly critical position to ensure that research is conducted ethically, protocols are strictly followed, regulatory and institutional requirements are met, and the rights and welfare of subjects are protected.

A large study sometimes requires a broad research team consisting of professionals and paraprofessionals with a wide range of expertise and experience. Whatever the composition of the research team, all of its members are responsible for the protection of human subjects in the research. In addition to fulfilling their own study-related duties, researchers at every level are responsible for ensuring that studies are conducted ethically and responsibly. Researchers involved in a particular research project have a strict obligation to notify the relevant IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or IRB determinations (§____.103 (b)(5)).

Coinvestigators, study coordinators, nurses, research assistants, and all other research personnel must:

- take measures necessary to protect the safety, rights, and welfare of human subjects;
- understand and act in accordance with accepted ethical principles;
- comply with all IRB findings, determinations, and requirements;
- adhere rigorously to all protocol requirements;
- promptly inform the PI of any protocol deviations or any changes made to eliminate immediate hazards to subjects that they become aware of;
- promptly inform the PI of all unanticipated problems involving risks to subjects or others that they become aware of;
- promptly inform the PI of all adverse events experienced by subjects that they become aware of;
- ensure that informed consent is properly obtained and documented if they are involved in the informed consent process;
- promptly notify the PI and/or the IRB of any serious or continuing noncompliance with regulatory requirements or the determinations of the IRB in any research in which they are involved; and
- implement the data and safety monitoring plan.

All members of the research team should be able to consult directly with the IRB chairperson or IRB professional staff, an institutional compliance officer, institutional legal counsel, or other resources about any matter or concern related to the protection of human research subjects.

E. The IRB

An IRB is a group of persons who have been formally designated by an institution (organization) that is conducting research to review the institution's research involving human subjects. By regulation, every IRB must have at least five members, with "varying backgrounds" to promote complete and adequate review of research activities commonly

conducted at the institution. The IRB must be sufficiently qualified through the experience, expertise, and diversity of its members—including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as commu-

nity attitudes—to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects (§____.107(a); 21 CFR 56.107(a)). (IRB membership requirements are detailed more specifically in Chapter 8.)

The IRB has the responsibility and authority for approving, requiring modification of (to secure approval), or disapproving human subjects research (§____.109(a); 21 CFR 56.109(a)). The IRB also has the authority to suspend or

terminate approval of research for any reason, including unexpected serious harms to subjects and noncompliance with the Common Rule or FDA regulations or other applicable government regulations; relevant institutional policies; or with its own findings, determinations, and requirements (§____.113; 21 CFR 56.113). (IRB roles and authorities are examined more closely in Chapter 7.)

In reviewing proposed research and in exercising continuing oversight of research, the IRB is specifically responsible for determining that:

- risks to subjects are minimized through sound research design;
- risks are reasonable relative to anticipated benefits;
- subject selection is equitable;
- adequate informed consent is obtained and appropriately documented;
- privacy and confidentiality protections are adequate;
- safety monitoring is adequate;
- additional safeguards are provided for vulnerable subjects (§____.111(b); 21 CFR 56.111(b)).

Criteria for IRB review and approval are discussed more thoroughly in Chapter 12.

IRBs should keep abreast of new developments in the field of human subjects protection. In addition, IRB members must be knowledgeable about current human subjects protection requirements and ethical considerations and should be provided with up-to-date initial and continuing education on a regular basis.

F. The IRB Administrator/ Director, Support Staff, and IRB Office

IRBs generally need both professional and administrative support. IRB professional members (i.e., IRB administrators/directors) are responsible for documenting IRB actions and determinations to ensure that they fully satisfy all regulatory requirements (see Chapter 9 for an extensive discussion of IRB administrative requirements). They also may be responsible for ensuring that IRB members, investigators, study coordinators, and other members of the research community are educated through formal training programs and day-to-day interactions regarding specific research proposals or human subjects protection issues.

Thus, IRB professional staff should have a detailed working knowledge of accepted ethical principles, relevant regulatory requirements, and institutional policies and procedures. Certification as an IRB professional (by obtaining Certification for IRB Professionals through the Council for Certification of IRB Professionals)

the IRB must be sufficiently qualified

IRB professional staff

and/or as an IRB manager (by obtaining Certification in IRB Management through the National Association of IRB Managers) is one mechanism that institutions might consider when building a quality HRPP (see Chapter 23). Regardless, continuing education of all personnel is essential for a strong HRPP.

IRB support staff provides administrative and clerical assistance and supplements the function and operation of IRBs under the direction of IRB professionals. To ensure that IRB support staff functions successfully, it is essential that they receive initial and continuing education about human subjects protection requirements.

Most institutions that operate an IRB find it appropriate to have a clearly identifiable IRB office, with the requisite resources to provide the IRB chairperson, IRB members, and research community with the support needed to fulfill their human subjects protection responsibilities. IRBs should be provided with secure storage space to ensure the confidentiality and privacy of IRB records.

The size of the IRB office and the ratio of professional staff to support staff must be commensurate with the nature and volume of research for which the office is responsible and the functions that the office performs. For example, an IRB office that conducts the institution's research protection education program for investigators and research staff or monitors good clinical practice (GCP; see Chapter 4) would require a larger staff than an IRB office whose duties are limited strictly to providing IRB support.

G. The Research Sponsor

According to the FDA regulations, a research sponsor is an individual, company, government agency, academic institution, private organization, or other organization that initiates and takes responsibility for a research investigation (21 CFR 50.3(e)). The sponsor is typically an organization that provides financial support for the research but does not actually conduct the research.

On occasion, an individual may both sponsor and conduct a research study. In such cases, the individual is referred to as a sponsor-investigator and must fulfill all of the responsibilities associated with each role (21 CFR 50.3(f)).

Responsibilities of research sponsors under the FDA regulations include the protection of human subjects by:

- maintaining the Investigational New Drug Application or Investigational Device Exemption;
- obtaining qualified investigators;

- providing necessary information and training for investigators, the research team, and others as required;
- monitoring the investigation;
- obtaining qualified monitors;
- controlling the investigational agent (drug, device, or biologic) being studied;
- reporting significant adverse events to the FDA and to investigators;
- maintaining and retaining accurate records.

**responsibilities
of research
sponsors**

In a broader, less regulatory sense, the word *sponsor* may refer to any organization that provides financial support, personnel, facilities, or other resources for research. In this sense, the departments and agencies that adhere to the Common Rule, for example, the National Institutes of Health or the Department of Veterans Affairs, might all be considered sponsors if they are conducting or supporting research subject to FDA regulation. As such, they are obligated to ensure protections of human subjects for their sponsored research. Each department and agency must also establish additional policies, procedures, and regulations to implement its human subjects protection requirements.

Private organizations that support research may also be considered sponsors. Unless the research is regulated by FDA, there is no federal statutory or regulatory mandate for private sponsors to require particular protections for human subjects. Nonetheless, private sponsors in the United States can choose to require evidence of IRB review or adherence to the Common Rule for the human subjects research they support.

H. Research Subjects

Research subjects also may be viewed as having responsibilities for the safe conduct of research. Potential research subjects should make every effort to comprehend the information researchers present to them and raise questions in order to make an informed decision about their participation in research. While participating, subjects also should make every reasonable effort to comply with the protocol requirements and inform the investigators of any unanticipated problems. (See Chapter 4 of IOM's *Responsible Research* [2003] for a detailed discussion of the responsibilities of research subjects.)

Subjects' Right to Withdraw

Research subjects always have the right to withdraw from research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.

Subjects are not obliged to explain their reasons for withdrawing from research, and they are not required to complete an exit interview or cooperate with follow-up activities.

I. Communities

Representatives of patient advocacy groups, ethnic groups, or geographic populations or other kinds of communities from which research subjects are recruited are playing an increasingly important role in the design and conduct of research, especially clinical research and genetic studies. Involvement of relevant groups prior to the design of the research and throughout the conduct of the research helps to ensure that:

- the goals and intended outcomes of the research meet genuine human needs;
- the risks of the research are viewed by the relevant community as justified relative to anticipated benefits;
- interventions and procedures used in the research are

considered reasonable and acceptable to the community of potential subjects;

- social and cultural norms and expectations are recognized and honored;
- potentially negative effects on the social or economic standing of patient groups, ethnic groups, and/or communities are recognized and protected;
- potential subject recruitment concerns and/or logistical problems are recognized and addressed.

Ideally, individuals, patient groups, ethnic groups, and communities are knowledgeable about local or specific issues or concerns related to research targeting specific patient or subject populations. As such, they are likely to be well suited to promote the best interests of those who might be asked to participate in the research. The potential role of communities in research, particularly in genetic research studies, is further discussed in Chapter 24.

Key Concepts:

Roles and Responsibilities for Protecting Human Subjects

- The ethical conduct of research is an individual, organizational, and shared responsibility.
- The standards underlying the responsibilities related to human subjects protection derive from nationally and/or internationally accepted ethical principles, government regulations, and the policies of individual organizations conducting research.
- Every institution conducting human subjects research should have an HRPP that provides the organizational structure and resources necessary to protect subjects.
- IRB activities make up only one component of an effective HRPP.
- Organizational commitment, authoritative leadership, initial and continuing education programs, and compliance oversight activities are all prerequisites for a successful HRPP.
- As the individual directly responsible for implementation of all aspects of the research, the researcher bears direct personal responsibility for protecting every research subject in his/her research.
- All members of the research team and all who are involved in the research enterprise are responsible for protecting human subjects.
- The IRB has the responsibility and authority for approving, requiring modification in (to secure approval), or disapproving research involving human subjects.
- Most institutions that operate an IRB find it appropriate to have a clearly identifiable IRB office to provide the IRB chairperson, IRB members, and the research community with the support needed to fulfill their human subjects protection responsibilities.
- Research subjects always have the right to withdraw from participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.
- Individuals representing patient groups, ethnic groups, and communities ideally are knowledgeable about relevant issues and, if consulted, are likely to promote the best interests of those who might be asked to participate in the research.

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Chapter 2

Selected Ethical Guidance for Human Subjects Protection

- A. Introduction
- B. The *Nuremberg Code*
- C. The *Declaration of Helsinki*
- D. The *Belmont Report*

Key Concepts

References



A. Introduction

This chapter provides a brief overview of three seminal twentieth-century documents that articulate principles for the ethical conduct of research involving human subjects—the *Nuremberg Code*; the *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*; and the *Belmont Report: Ethical Principles for the Protection of Human Research Subjects* (the entire *Belmont Report* appears in Appendix A). Contextual information about the historical events that led to the formulation of these codes and principles is also provided. Similar principles have been articulated and expanded in later codes and guidelines developed by national and international organizations (Table 2.1) and professional societies. Although virtually all codes incorporate the basic concepts of voluntary participation and informed consent, each has its own particular areas of emphasis or concern. (Other international standards, including the *International Conference on Harmonisation Good Clinical Practice* guideline, are discussed in greater depth in Chapter 21 [ICH 1996]).

The *Nuremberg Code* is a set of ethical principles developed by a U.S. military tribunal responsible for bringing

to justice Nazi doctors who carried out atrocious medical experiments on human beings during World War II as part of the Nazi Holocaust (Nuremberg 1949). The *Nuremberg Code* formalized the concepts of consent, right to withdraw, and the weighing of risks and benefits and provided a foundation for the formulation of subsequent medical ethics doctrines.

The *Declaration of Helsinki* was issued by the World Medical Association (WMA) in 1964 and subsequently amended five times, most recently in 2000. It emphasizes the physician's primary responsibility as that of safeguarding the health of the people and asserts that "the well-being of the human subject should take precedence over the interests of science and society."

The *Belmont Report* was published by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission 1979). It defined ethical principles associated with the conduct of human subjects research and served as the framework for the development of the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) and FDA regulations (21 CFR 50 and 56).

Table 2.1
Selected Human Subjects Protection Guidelines

Title of Guideline	Issuing Organization
<ul style="list-style-type: none"> • The <i>Declaration of Helsinki</i> 	WMA (2000) (www.wma.net/e/policy/b3.htm)
<ul style="list-style-type: none"> • The <i>Belmont Report</i> 	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979) (United States) (http://ohsr.od.nih.gov/guidelines/belmont.html)
<ul style="list-style-type: none"> • <i>International Conference on Harmonisation Guideline for Good Clinical Practice</i> 	International Conference on Harmonisation (ICH) (1996) (www.fda.gov/cder/guidance/959fnl.pdf)
<ul style="list-style-type: none"> • <i>International Ethical Guidelines for Biomedical Research Involving Human Subjects</i> 	Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (2002) (www.cioms.ch/frame_guidelines_nov_2002.htm)
<ul style="list-style-type: none"> • <i>International Guidelines for Ethical Review of Epidemiological Studies</i> 	CIOMS (1991) (http://www.cioms.ch/frame_1991_texts_of_guidelines.htm)
<ul style="list-style-type: none"> • <i>Operational Guidelines for Ethics Committees That Review Biomedical Research</i> 	WHO (2000) (www.who.int/tdr/publications/publications/pdf/ethics.pdf)
<ul style="list-style-type: none"> • <i>Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products</i> 	WHO (1995) (www.who.int/medicines/library/par/ggcp/GGCP.shtml)
<ul style="list-style-type: none"> • <i>Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine</i> 	Council of Europe (1997) (www.conventions.coe.int/Treaty/en/Treaties/Html/164.htm)
<ul style="list-style-type: none"> • <i>Medical Research Council Good Clinical Practice in Clinical Trials</i> 	Medical Research Council (1998) (United Kingdom) (http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002416)
<ul style="list-style-type: none"> • <i>Ethical Guidelines for Biomedical Research on Human Subjects</i> 	Indian Council of Medical Research (2000) (http://icmr.nic.in/ethical.pdf)
<ul style="list-style-type: none"> • <i>Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans</i> 	Medical Research Council, Natural Sciences and Engineering Council, Social Sciences and Humanities Research Council (Canada) (1998) (www.ncehr-cnerh.org/english/code_2/)

B. The Nuremberg Code

The modern history of human subjects protection begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related research experiments. These experiments routinely exposed captive subjects to grossly inhumane interventions, causing extreme pain and suffering and often resulting in death.

That these medical experiments were cruel is obvious: they included severe oxygen deprivation, extended exposure to extreme temperatures and toxic agents of all kinds, and the infliction of wounds and amputations. One experiment, involving identical twin children, purposely subjected one twin to a harmful substance, tracked the effect of the intervention to death, and then sacrificed the healthy twin for a comparative autopsy. Despite being members of a medical community with relatively advanced ethical standards, the Nazi doctors were nonetheless apparently

able to justify these experiments to themselves in the name of science and as beneficial to society or at least to the war effort (Rothman 1991).

In reaction to these atrocities, the Nuremberg Military Tribunal developed 10 principles, known as the *Nuremberg Code*. The first of these principles stipulates that the “voluntary consent of the human subject is absolutely essential” and makes clear that such consent is characterized by the legal capacity to exercise free choice without any constraint or coercion and with sufficient comprehension to make an informed decision. Making a free choice requires an understanding of the nature, duration, purpose, and methods of an experiment and of all reasonably expected inconveniences and hazards that may be associated with it. Moreover, each individual “who initiates, directs, or engages in the experiment” must

“voluntary consent of the human subject is absolutely essential”

bear personal responsibility for ensuring the quality of consent. It is important to recognize, however, that even with informed consent, the Nazi experiments would not have been ethical and that the *Nuremberg Code* enumerates many other important principles.

Other principles of the *Nuremberg Code* (provided in Table 2.2) require that risks be minimized and justified relative to the anticipated results and that subjects be at liberty to end their participation when the subject deems it to be necessary.

C. The Declaration of Helsinki

The *Declaration of Helsinki* is an official policy document of WMA, a global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa), and 2000 (Edinburgh, Scotland).

The current version of the *Declaration of Helsinki* consists of 32 principles divided into three sections:

Table 2.2
The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility that may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required, through all stages of the experiment, of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.
10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10, Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949.

Medical Care. In addition to emphasizing the *Nuremberg Code* principles requiring voluntary consent, freedom to withdraw, avoidance of injury, and the

weighing of risks against anticipated benefits, the *Declaration of Helsinki* makes clear that the “well-being of the human subject should take precedence over the interests of science and society” (WMA 2000, A.5) (see Table 2.3). It also states that medical research involving human subjects should be subject to review, approval, and oversight by an independent ethics committee, such as an Institutional Review Board (IRB) or its equivalent.

The *Declaration of Helsinki* addresses the need to provide special protections for vulnerable populations of subjects, including economically and medically disadvantaged persons, persons for whom the research is conducted within the context of the provision of health care, and persons under duress. Physician-investigators are warned to be “particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress” (WMA 2002, B.23). In such cases, the *Declaration of Helsinki* recommends that informed consent should be obtained by “a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship” (WMA 2002, B.23).

Persons who are not capable of providing (or refusing) consent on their own also deserve special protection. The Common Rule requires investigators to obtain informed consent from the subject’s legally authorized representative to include a research subject who is a minor, is legally incompetent, or is otherwise unable to give consent. The *Declaration of Helsinki* states that these groups “should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot be performed on legally competent persons” (WMA 2002, B. 24).

Changes made to the last version of the *Declaration of Helsinki* have been controversial. In 2000, the following principles were added to the document:

- The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.
- At the conclusion of a study, every patient entered into the study should be assured access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.

Some researchers see these principles as severely limiting their ability to conduct important clinical trials that involve subjects in developing countries and/or placebo-controlled study designs. Researchers have argued that it is not always possible, or even desirable, to include the best current or best proven therapeutic methods in research conducted in developing countries or to ensure that subjects in such countries will have access to the best methods after the study has ended. They have pointed out that in many developing countries, national infrastructure and resources are wholly inadequate to the task of providing patients with therapeutic methods that are effective and available in the developed world (Kass and Hyder 2001).

Moreover, some researchers assert that patients in developing countries can benefit only from research that examines interventions that can realistically be delivered, given the national infrastructure and resources available. They assert that it is unethical to involve these populations in research on practices from which they cannot realistically benefit, including research on certain current best or best proven treatments that would only be feasible in more developed countries (Glantz et al. 1998). Likewise, researchers have argued that, even in developed countries, testing new therapies against the best proven therapy is not always the best scientific or practical approach.

In 2002, WMA clarified that “placebo-controlled trials may be ethically acceptable, even if proven therapy is available” where “compelling and scientifically sound methodological reasons” make them necessary to determine safety or efficacy, or when subjects receiving placebos will not be exposed “to any additional risk or serious or irreversible harm.”

Nonetheless, this issue remains controversial, as some observers believe the clarification compromises the basic principle that the “well-being of the human subject should take precedence over the interests of science and society” (WMA 2002).

Table 2.3**The Declaration of Helsinki, World Medical Association, 2000****A. INTRODUCTION**

1. The World Medical Association has developed the *Declaration of Helsinki* as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The *Declaration of Geneva* of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research that ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subjects should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research, and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this *Declaration*.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and, where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this *Declaration*.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

(continues on following page)

20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent or physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations, and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this *Declaration* should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists. (See footnote.)
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study.
31. The physician should fully inform the patient as to which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, reestablishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this *Declaration* should be followed.

Footnote: Note of clarification on Paragraph 29 of the WMA *Declaration of Helsinki*

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method; or
- where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm, all other provisions of the *Declaration of Helsinki* must be adhered to, especially the need for appropriate ethical and scientific review.

D. The Belmont Report

The *Nuremberg Code* had little or no immediate impact within the American scientific community. Although publicly available (after a brief period as a classified document), the *Nuremberg Code* was considered relevant only for egregious wrongdoers such as the Nazi doctors. It was thought that the underlying integrity and altruism of medical practitioners in the United States would prevent abuses of research subjects from ever occurring here (Rothman 1991).

Although a few reports of ethically questionable research involving human subjects had been reported in the popular press, protection of human research subjects did not receive widespread attention from the American public until the details of the U.S. Public Health Service (PHS) Syphilis Study at Tuskegee became widely known in the early 1970s.

The infamous PHS *Study of Untreated Syphilis in the Negro Male* was a 40-year research study conducted in Macon County, Alabama, by PHS physicians designed to gain an understanding of the natural history of untreated latent syphilis. Initiated in 1932, the research targeted poor African-American sharecroppers suffering from syphilis and was presented to subjects as a study of “bad blood” (Jones 1993). The study continued until a July 26, 1972, *New York Times* story, “Syphilis Victims in U.S. Study Went Untreated for 40 Years,” exposed it as “the longest non-therapeutic experiment on human beings in medical history” (Heller 1972).

The PHS research involved 399 men with latent syphilis and a control group of 201 men without the disease. During the course of the research, participation was encouraged with powerful incentives such as free meals, free medical examinations, and free burial insurance, the last of which proved to be a particularly effective inducement for this impoverished group.

After penicillin was identified as a highly effective treatment for syphilis and became widely available, to preserve the study, the investigators breached ethical codes even further by taking steps to ensure that the subjects were denied access to the treatment.

The PHS study, which resulted in real physical and dignity harm to subjects and their families, constituted patent exploitation of vulnerable subjects by government officials and researchers. This disregard of ethical standards by numerous investigators over a 40-year period severely damaged the overall credibility of medical research among

African-Americans, creating a climate of suspicion that remains to this day.¹

Revelations about the PHS syphilis study led to Senate hearings, chaired by Edward M. Kennedy and in 1974 resulted in legislation (Title II of the National Research Act [PL 93-348]) mandating regulations to protect human subjects. The legislation also called for the creation of a national commission to examine ethical issues related to human subjects research. From 1974 to 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued a number of reports, most of which focused on the involvement of vulnerable subjects in research.

**National Commission
for the Protection of
Human Subjects of
Biomedical and
Behavioral Research**

The National Commission’s final and most influential report (1979), the *Belmont Report*, provides critical guidance regarding the boundaries between biomedical research and the practice of medicine, defines and explains three fundamental ethical principles, and applies the principles to the conduct of research. The *Belmont Report* is now recognized as a seminal document in defining the ethical responsibilities associated with conducting human subjects research.

The *Belmont Report* defines three specific ethical principles for the protection of human subjects:

- (1) **respect for persons**, operationalized by obtaining informed consent,
- (2) **beneficence**, operationalized by minimizing possible harms and maximizing possible benefits, and
- (3) **justice**, operationalized by the fair or equitable selection of subjects.

These principles form the basis of the Common Rule, as well as the equivalent Department of Health and Human Services and Food and Drug Administration regulations, and were developed out of a growing awareness over the past 50 years of the need to minimize risks and respect the rights and welfare of those who volunteer for research.

Practice Versus Research

The *Belmont Report* defines medical or behavioral practice as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success” (National Commission 1979, 1). By contrast, research is defined as “an

¹ On May 6, 1997, nearly 20 years after the *New York Times*’ exposé and 65 years after the Public Health Service study began, surviving subjects and the members of the Tuskegee Syphilis Study Legacy Committee gathered at the White House to witness a long-awaited apology from the President of the United States.

activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge” (1979, 1).

The distinction between practice and research is important because both researchers and subjects need to understand that the primary consideration in research is to make a contribution to generalizable knowledge. As a result, treatment of a particular individual is determined by the research protocol, rather than by clinical characteristics alone. The important difference as articulated in the *Belmont Report* is that the goal of research is generalizable knowledge and the goal of clinical care is the best interests of the individual patient. The *Belmont Report* acknowledges, however, that the boundary between practice and research is blurred because both often occur together and because notable departures from standard practice are often called experimental. Such departures may or may not be research, but the *Belmont Report* recommends that radically new procedures should be made the object of formal research at an early stage.

In general, if there is an element of research in an activity, that activity should undergo review for the protection of human subjects.

Respect for Persons

The ethical principle of respect for persons incorporates two convictions:

- Individuals should be treated as autonomous agents.
- Persons with diminished autonomy are entitled to protection.

An autonomous person is one who is capable of self-determination. Respect for persons in a research context recognizes the individual’s right to make free choices and exercise personal autonomy.

Individuals who are not capable of self-determination have diminished autonomy. Respect for persons extends protection in proportion to the risk of harm, the likelihood of benefit, and the extent of diminished autonomy. Some individuals need extensive protection from research participation (e.g., children, individuals with cognitive disorders), while others only need assistance in understanding consequences and undertaking actions freely.

Specific application of respect for persons in research results in the obligation to obtain informed consent from research subjects. The process of informed consent includes three essential elements: information, comprehension, and voluntariness.

Information provided during the informed consent process must include items such as the research procedure, purpose, risks, anticipated benefits, and alternative procedures (see Chapter 12 for an extensive discussion of the informed consent process). However, simply listing these items is not sufficient. The nature and extent of the information provided should be tailored to include whatever a reasonable individual would wish to know before deciding whether or not to participate in the particular research protocol.

The manner and context of the presentation, as well as the prospective subject’s intelligence, rationality, maturity, language, health status, and education level, all affect comprehension of informed consent information. Investigators must tailor the presentation of informed consent information to the subject’s capacities, and special provisions may be needed when comprehension is severely limited (see Chapter 12). Voluntariness of consent can occur only when the prospective subject is free from coercion and undue influence.

voluntariness of consent

Beneficence

The ethical principle of beneficence aims to secure the well-being of other persons through two obligations: doing no harm and maximizing possible benefits and minimizing possible harm.

maximizing possible benefits and minimizing possible harm

Attempting to satisfy these two obligations in a research context often produces a dilemma. It is sometimes impossible to avoid harm altogether. In addition, action and inaction both can produce harm, and it may be difficult to predict which will result in greater or lesser harm. As a result, beneficence usually requires weighing uncertain outcomes. Moreover, beneficence also requires weighing individual risks and benefits against societal risks and benefits. Decision making in this regard is clearly affected by personal and cultural values.

Given the difficulties in weighing risks with potential benefits, the *Belmont Report* emphasizes that review committees conduct a “systematic, nonarbitrary” assessment of risks and benefits that minimizes “misinterpretation, misinformation, and conflicting judgments” through a step-by-step analysis that includes:

- determination of the validity of the presuppositions of the research;
- clarification of the nature, probability, and magnitude of risk;
- critical review of the reasonableness of the investigator’s estimates as judged by other available information; and

- a final assessment of justifiability, reflecting the following considerations:
 - brutal or inhumane treatment is never justified,
 - risks must be reduced as much as possible,
 - risk of serious impairment requires extraordinary justification,
 - the involvement of vulnerable populations must be clearly demonstrated as warranted, and
 - risks and benefits must be described thoroughly in the informed consent process (see Chapter 11 for a discussion of the review process).

Justice

The *Belmont Report* addresses the justice of, “Who ought to receive the benefits of research and bear its burdens?” The report notes that there are several widely accepted formulations of just ways in which to distribute burdens and benefits: (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit (see Table 2.4).

There are historical examples of unjust research, where the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients.

In a research context, justice requires that the burdens and

burdens and benefits of research should be shared fairly

benefits of research be shared fairly among all societal groups. For example, the benefits of publicly funded research should not be

limited to particular economic or social groups. Likewise, the burdens of research should not be borne by groups that are unlikely to benefit from the application of the knowledge gained in the research.

According to the *Belmont Report*, justice translates in practical application to fair procedures and outcomes in the selection of subjects at both the individual and social levels. At the individual level, justice dictates that investigators should not “play favorites” in recruiting subjects for potentially beneficial research or single out vulnerable populations for research with higher risk. In addition, IRBs and investigators must be mindful of unintentional injustices that may arise from social, racial, sexual, and cultural biases that are pervasive in their social setting.

At the societal level, justice requires that distinction be drawn between classes of subjects that should and should not participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. For example, potentially risky research is typically performed with adults instead of, or prior to, being performed with children. Moreover, groups that are medically, socially, or economically disadvantaged should not be recruited into research studies because they are readily available or more subject to coercion or undue influence.

Table 2.4
The Belmont Report Principles Summarized*

Principle	Application in Research
Respect for Persons <ul style="list-style-type: none"> • Autonomy • Protection 	Informed Consent <ul style="list-style-type: none"> • Information • Comprehension • Voluntariness
Beneficence <ul style="list-style-type: none"> • Do no harm • Maximize benefit/minimize harm 	Risks Versus Potential Benefits <ul style="list-style-type: none"> • Systematic assessment • Independent reviewers
Justice <ul style="list-style-type: none"> • Individual justice • Social justice 	Equitable Selection of Subjects <ul style="list-style-type: none"> • Individual fairness • Social fairness

*See Appendix A for complete text.

Key Concepts:

Selected Ethical Guidance for Human Subjects Protection

- The *Nuremberg Code* is a set of ethical principles developed by the U.S. military court responsible for bringing the Nazi doctors to justice after World War II. It formalized the concepts of voluntary consent, subjects' freedom to withdraw, and the weighing of risks and benefits for research.
- First published in 1964, the *Declaration of Helsinki* makes clear that the "well-being of the human subject should take precedence over the interests of science and society." The current *Declaration of Helsinki* emphasizes independent review of research, special protections for vulnerable populations of subjects, informed consent, risk/benefit analysis, use of placebo controls, and access to the best proven care for patients after the study.
- The protection of human research subjects did not receive widespread attention from the American public until the details of the U.S. PHS Syphilis Study at Tuskegee became widely known in the early 1970s.
- The *PHS Syphilis Study* involved 399 African-American men with latent syphilis and a control group of 201 men without the disease. In a reprehensible breach of ethics, to preserve the continuity of the study, PHS investigators took specific steps to ensure that subjects were denied access to effective treatment, even after penicillin was identified as a highly effective treatment for syphilis and became widely available.
- The *Belmont Report* provides critical guidance regarding the boundaries between clinical research and clinical practice, defines and explains three fundamental ethical principles, and applies the principles to the conduct of research.
 - The distinction between practice and research is important because both researchers and subjects should understand that the primary goal in research is the contribution to general knowledge, rather than treating or caring for the individual patient-subject.
 - The ethical principle of respect for persons incorporates two convictions: (1) individuals should be treated as autonomous agents and (2) persons with diminished autonomy are entitled to protection.
 - Respect for persons results in the obligation to obtain informed consent, which includes three essential elements: (1) information, (2) comprehension, and (3) voluntariness.
 - The ethical principle of beneficence acts to secure the well-being of other persons through two obligations: (1) doing no harm and (2) maximizing benefits and minimizing possible harm.
 - The ethical principle of justice requires fair procedures and outcomes in the selection of subjects at both the individual and societal levels.

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Chapter 3

The Regulatory Mandate to Protect Human Subjects

- A. Introduction
 - B. Understanding the Regulatory Process
 - C. Federal Policy (Common Rule) for the Protection of Human Subjects
 - D. Food and Drug Administration (FDA) Regulations
 - E. Differences Among Food and Drug Administration, Department of Health and Human Services (DHHS), and Common Rule Regulations
 - F. Increased Interest in Human Research Protections
- Key Concepts**
References



A. Introduction

This chapter briefly summarizes the history and scope of the federal regulations governing research involving human subjects. Subsequent chapters explore the substantive and procedural requirements of the regulations. Chapter 16 describes in greater detail the regulations of the Food and Drug Administration (FDA).

Currently, there are three primary sources of federal regulatory protection for human subjects:

- The Federal Policy for the Protection of Human Subjects (the Common Rule), codified or otherwise adopted by 18 executive branch departments and agencies, is identical to Subpart A of 45 CFR Part 46 (56 *Federal*

Register 28003).¹ (See Appendix C.)

- FDA Informed Consent and Institutional Review Board (IRB) regulations at 21 CFR Parts 50 and 56.² (See Appendix D.)
- Department of Health and Human Services (DHHS) regulations for the protection of human subjects, codified at 45 CFR Part 46, and including Subparts A through E.³

Direct federal authority over the conduct of human subjects research extends only to research that is either (1) conducted or supported by the one or more of the federal departments or agencies that have adopted the Common Rule (see Table 3.1) or (2) regulated as research under a spe-

¹ Each codification of the Federal Policy for the Protection of Human Subjects by a department or agency is equivalent to 45 CFR 46.101-46.124 (Subpart A), the Department of Health and Human Services (DHHS) codification. Each signatory to the Federal Policy, also called the Common Rule, codified the regulations separately; however, the individual sections of the regulations are identical to 45 CFR Part 46, Subpart A (except in their initial reference number), with the exception of the regulations of the Food and Drug Administration (FDA), in which the reference number and sometimes the language differ in some key areas (56 *Federal Register* 28002, June 18, 1991). Throughout this manual, the codification will be referred to as §____.XXX when citing the regulatory requirements of the Common Rule. Anyone looking at any version of the Common Rule, regardless of the agency that has signed on, will be able to recognize the codification using this format. The FDA requirements will also be cited. Throughout this manual, when both the Common Rule and FDA regulations are applicable, the Common Rule citation will appear first, followed by the FDA citation—for example, (§ .108(b); 21 CFR 56.108(c)). DHHS also adheres to Subparts B through D, which address special protections for vulnerable populations (discussed later in this manual). 45 CFR Part 46 Subparts A through D are available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>. Some departments and agencies have also incorporated some or all of the subparts into their policies.

² See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm>.

³ See <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

cific federal statute. In addition to the regulatory requirements, federal agencies might have additional requirements for research conducted with their funds (see, for example, Chapter 25, “Human Gene Transfer Research”).

Thus, for example, research supported under a grant from the U.S. Department of Education would be subject to its human subjects protection requirements, (i.e., the Common Rule codified for the Department of Education at 34 CFR Part 97)⁴ and certain additional requirements imposed by the Department of Education as a condition of receiving funds from that department. Recipients of federal research funds must be cognizant of all conditions applied to the receipt of those funds.

Privately sponsored research involving an investigational drug, device, or biologic is subject to the FDA human protection regulations because FDA regulates such research under the Food, Drug, and Cosmetics Act. Research involving investigational drugs, devices, or biologics that is conducted or supported by one of the departments or agencies that adhere to the Common Rule is governed both by the requirements of the supporting department or agency and by FDA regulations. For example, if an academic investigator receives funds from the National Institutes of Health (NIH) for research involving an investigational new drug, he/she would have to comply with Department of Health and Human Services (DHHS) requirements as well as FDA requirements.

Some research is not subject to federal regulation in any way. Human subjects research that is neither regulated by FDA or another federal department or agency, nor supported or conducted by the federal departments or agencies that have adopted the Common Rule, is not automatically subject to federal oversight. However, research institutions may voluntarily extend the federal protections to all of their human subjects research, regardless of the source of research funding, and formally make this commitment as part of the human subject assurance of compliance that they submit to the federal government (see Chapter 5).

It is also important to note that the federal regulations rely on state law in certain areas (e.g., for the definitions of *child* and *legally authorized representative*) and that some states (e.g., California, Maryland) have statutes or regulations that cover the conduct of research, including issues such as privacy and ownership of biological specimens. IRBs and investigators should be aware of any applicable state or local laws or regulations in addition to the federal requirements.

B. Understanding the Regulatory Process

In addition to ensuring compliance with all applicable regulations, institutions, IRBs, and investigators must be alert for new regulations or guidance documents that are periodically provided by federal authorities. Developing regulations goes by the name of *rulemaking*. By law, anyone can participate in the rulemaking process by submitting comments on regulations that are proposed by a regulatory agency. When a regulatory agency plans to issue a new regulation or revise an existing one, it places an announcement in the *Federal Register* on the day the public comment period begins. The *Federal Register* is available at many public libraries and colleges, and on the Internet.

The *notice of proposed rulemaking* or proposed rule describes the planned regulation and provides background on the issue. The portion that includes description and rationale is considered the *preamble*. It also gives the address for submitting written or electronic comments, a contact for more information and the deadline for public comments. Usually the comment period lasts 60 days, although there are exceptions.

**notice of
proposed
rulemaking**

The regulatory agency will sift through all the comments, assess them on their relative merits and on any evidence provided, and use the comments to reconsider all or parts of the proposed revision or new regulation. Sometimes the nature of the comments may be such that the agency reconsiders the proposed rule and publishes it again for an additional round of comments. When the agency has completed its final review of all the comments, redrafted the regulation, and received internal approval on the final document, the *final rule* is ready to be published in the *Federal Register*. The final rule will then be incorporated, or codified, into the *Code of Federal Regulations* (CFR).

final rule

A final rule has an effective date, at which time all members of the regulated community must be in compliance with the regulation or possibly face sanctions by the agency.

Sometimes, an agency will publish an earlier proposal than a proposed rule, while it is still thinking about what to do about the regulated activity. This is called an *advance notice of proposed rulemaking*, which is intended to gather information from relevant constituencies on how a regulation should be written. It may combine the *Federal Register* notice with public meetings to solicit advice on how to proceed.

⁴ See www.access.gpo.gov/nara/cfr/waisidx_00/34cfr97_00.html.

One other variation on the rulemaking process is the *interim rule*. An interim rule is published when a regulatory agency must issue a regulation for some reason (for example, enactment of a new law or in response to a serious event that must be addressed quickly) but has not come to a final decision on the details of how that regulation should be structured, although it still wishes to solicit public comment. The solution is an interim rule, which stipulates all the regulations that must be complied with at the effective date but which also provides for a public comment period that enables to agency to receive input that it will use in considering whether to make changes prior to issuing a final rule. The key distinction between interim and proposed rules is that an interim rule requires immediate compliance before a final rule is issued (as of the effective date), while a proposed rule does not.

Once final, the CFR is organized by general topic. It is divided into 50 *titles* that represent broad areas subject to federal regulation. Each title is further divided into *chapters*, which usually bear the name of the agency responsible for issuing the regulations. Chapters are subdivided into *parts* and finally into *sections*.

A typical citation of a regulation in the CFR looks like this:

21 CFR 50.1 (1980) or 21 CFR § 50.1 (1980)

“21” refers to the *Title* number (Title 21, Food and Drugs)

“CFR” is the standard abbreviation for the *Code of Federal Regulations*.

“50” refers to *Part* number 50 within Title 21 (Protection of Human Subjects).

“50.1” or “§50.1” refers to a more specific *Section* within Part 50, in this case “Scope.”

“1980” is the year in which this version of the CFR was published.

Regulations can be difficult to understand or somewhat vague regarding what is expected of the regulated community. Occasionally, an agency will issue follow-up advice to the regulated community on what it believes is appropriate compliance with a particular regulation. This advice is called *guidance*. The availability of a guidance document is often published in the *Federal Register*, but, more often than not, the regulated community will need to periodically visit the agency’s Web site to learn about the release of guidance documents.

Guidance documents are not regulations. Rather, they represent the agency’s current thinking on a topic. Guidance documents do not bind the agency or the public, but they provide good information on approaches the agency believes the regulated community should take to be in compliance, and they should be reviewed carefully. An alternative approach to that provided in the guidance may be used if the approach satisfies the requirements of the applicable regulations. However, the burden falls on the regulated community to demonstrate to the agency that its alternative is as good as or better than that provided in the guidance.

Some guidance documents are issued as final documents at the outset (Level 2), while others are issued in draft form to solicit public comment (Level 1). Typically, Level 1 guidance involves matters of significant impact or complexity, or the initial interpretation of regulations, and thus warrants preliminary comment from the public before implementation. Nonetheless, both types of guidance documents will include the public comment solicitation, although Level 1 guidance documents are not considered in effect until after the comments have been received and reviewed and a final guidance is issued.

One final type of regulatory document exists called the *guideline*. The International Conference on Harmonisation (ICH) issues guidelines, such as the ICH *Good Clinical Practice* guideline (E6) (ICH 1996). Although FDA regulations no longer recognize the term *guideline*, the agency’s practice is to accept ICH guidelines as draft and final guidance.

Because of the size of its budget relevant to human subjects research, DHHS policies for such research are widely recognized, although other agencies also have longstanding policies for protecting human subjects. For example, as early as 1925, the Department of Defense required that only volunteers be used in infectious disease research (U.S. Department of the Army 1925). However, because it was one of the first agencies to develop a more comprehensive and systematic policy for human subjects protections, the history of the DHHS regulations is summarized here.

In 1953, the newly created Clinical Center at NIH introduced a requirement for group consideration of proposed human subjects research (only for those studies involving healthy volunteers) and emphasized protections for normal healthy volunteers. This marked the first written federal policy for protecting human subjects and introduced the mechanism of independent group review to ensure such protections, thus foreshadowing the concept of the modern IRB.

During the 1950s through the early 1970s, a number of research projects demonstrated serious problems with the human subjects protections then in place. Articles published by Henry Beecher in 1959 in the *Journal of the American Medical Association* and in 1966 in the *New England Journal of Medicine* described a number of questionable research studies, including:

- the transplantation of an animal kidney into a human patient;
- the injection of live cancer cells into seriously ill patients;
- the exposure of unwitting individuals and groups to radiation;
- the “bugging” by social scientists of jury deliberations;
- the identification of persons observed making homosexual contacts;
- psychology research on obedience to authority and social conformity (Beecher 1966; Beecher 1959).

In response to these articles and growing concerns about the adequacy of protections, in 1966 the U.S. Public Health Service (PHS) issued a policy and procedure order (PPO #129) requiring the review of grantees’ clinical research search by a committee of institutional associates that would assure an independent determination of:

- the rights and welfare of the subjects;
- the appropriateness of the informed consent process;
- the risks and potential benefits of the investigation

The Office for Protection from Research Risks (OPRR), an office within NIH, was created as an outgrowth of NIH’s Institutional Relations Branch in 1972 and would eventually become the principal federal entity besides FDA responsible for the oversight of human subjects research sponsored or conducted by what was then called the Department of Health Education and Welfare (DHEW).

After the infamous Tuskegee Syphilis Study (see Chapter 2) came to light, Congressional action in 1974 resulted in the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission). That same year, DHEW codified its human subjects protection policy as regulation at Title 45 CFR Part 46.

In accordance with the recommendations of the National Commission, subparts were added to the DHEW regulations for the protection of human subjects to confer additional pro-

tections for fetuses, pregnant women, and human *in vitro* fertilization (45 CFR Part 46, Subpart B 1975; revised as protections for pregnant women, human fetuses, and neonates in 2001) and prisoners (45 CFR Part 46, Subpart C 1978) involved in research.

**additional
protections**

In 1979, the National Commission issued its recommendations for human subjects protections in what has come to be known as the *Belmont Report* (National Commission 1979) (see Chapter 2 for a lengthier discussion of this report). The basic DHHS regulatory protections for human subjects at 45 CFR Part 46, Subpart A, were revised in January 1981 in accordance with the recommendations of the National Commission, as were FDA’s regulations. The 1981 revision resulted in regulatory provisions that have remained with only a few changes as the current DHHS/FDA regulations.

Finally, in accordance with the recommendations of the National Commission, another subpart was added to the regulations to confer additional protections for children involved in research (Subpart D 1983) (McCarthy 2001; 1987).⁵

C. Federal Policy (Common Rule) for the Protection of Human Subjects

With the completion of the National Commission’s work in 1978, President Jimmy Carter appointed the President’s Commission for the Study of Ethical Problems in Biomedical and Behavioral Research (the President’s Commission).

**the
President’s
Commission**

In 1981, the President’s Commission recommended the adoption of uniform regulations for all federally supported human subjects research (President’s Commission 1981). The President’s science advisor appointed an ad hoc committee for this purpose in 1982, and a proposed Model Federal Policy for the Protection of Human Subjects was published in the *Federal Register* for public comment in 1986.

The recommendation by the President’s Commission for uniform federal human subjects regulations was issued in final form in 1991 with the adoption of the Federal Policy for the Protection of Human Subjects (Common Rule). The Common Rule is the same as Subpart A of the DHHS regulations at 45 CFR 46. Federal departments and agencies currently implementing the Common Rule are listed in Table 3.1.

⁵ Journal of Clinical Research and Drug Development. Ethical and Policy Issues in Research Involving Human Participants, Volume 2. See <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

Table 3.1
Federal Common Rule Departments and Agencies

Department/Agency	CFR Citation
<ul style="list-style-type: none"> • Department of Agriculture • Department of Energy • National Aeronautics and Space Administration • Department of Commerce • Consumer Product Safety Commission • International Development Cooperation Agency, Agency for International Development • Department of Housing and Urban Development • Department of Justice • Department of Defense • Department of Education • Department of Veterans Affairs • Environmental Protection Agency • Department of Health and Human Services • National Science Foundation • Department of Transportation • Central Intelligence Agency 	<p>7 CFR Part 1c 10 CFR Part 745 14 CFR Part 1230 15 CFR Part 27 16 CFR Part 1028 22 CFR Part 225</p> <p>24 CFR Part 60 28 CFR Part 46 32 CFR Part 219 34 CFR Part 97 38 CFR Part 16 40 CFR Part 26 45 CFR Part 46 45 CFR Part 690 49 CFR Part 11 Executive Order 12333</p>

Although each of the Common Rule departments and agencies is responsible for its own interpretation and enforce-

16 Common Rule departments and agencies

ment of the Common Rule relative to the research it supports, every effort is made to achieve consistency in interpretation. To this end, implementation of the Common Rule is coordinated among the 16 Common Rule departments and agencies

by the Human Subjects Research Subcommittee, a subcommittee of the Health Committee on Science of the National Science and Technology Council in the Executive Office of the President.

Each department or agency maintains a human subjects protection program that provides information and assistance to the researchers it supports, as well as oversight of compliance with the Common Rule. The size and scope of these programs vary considerably, depending in part on the amount of human subjects research that the department or agency supports.

D. FDA Regulations

FDA's regulatory history dates back to 1906 with the passage of the Federal Food and Drugs Act,⁶ which added regulatory functions to the agency's original scientific mission within the U.S. Department of Agriculture. On June 25, 1938, the Federal Food, Drug, and Cosmetic Act was signed by President Roosevelt. Since 1953, FDA has resided in what is now DHHS.

Congressional concern beginning in the late 1950s about the safety and efficacy of marketed drugs led in to a major revision of the Food, Drug, and Cosmetic Act in 1962. The Kefauver-Harris Amendments strengthened FDA's oversight responsibility and authority and, among other things, required informed consent from subjects enrolled in drug and device research.⁷

FDA's mission is to promote and protect the public health by ensuring that safe and effective products reach the market in a timely way and by monitoring products for continued

⁶ See www.fda.gov/opacom/laws/wileyact.htm.

⁷ See <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm> for an explanation of the major changes.

safety after they are in use. FDA's work is a blending of law and science aimed at protecting consumers and regulating the development of new products.

The agency enforces the Food, Drug, and Cosmetic Act by regulating clinical investigations conducted on test articles such as drugs, biologics, and medical devices. Research conducted on new products that are designed to treat human conditions or diseases is scrutinized by FDA reviewers for safety and effectiveness before the new products can be made available to consumers (see Chapter 16 for an extensive discussion of FDA's regulations).

In 1981, when the DHHS regulations providing protections for human subjects at 45 CFR Part 46 were revised in accordance with the recommendations of the National Commission, FDA regulations also were revised to produce almost identical regulations regarding informed consent (21 CFR Part 50) and IRB review (21 CFR Part 56).⁸

FDA's human subjects protection regulations at 21 CFR Part 50 (for informed consent) and 21 CFR Part 56 (for IRB review) apply to clinical investigations that support applications for research or marketing permits for FDA-regulated products, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products (see Chapter 16 for more detail on FDA regulations).

FDA regulations for clinical investigations

Additional FDA regulations that are relevant to the protection of human subjects address Investigational New Drug Applications (INDs) (21 CFR Part 312),⁹ Biological Products (21 CFR Part 600),¹⁰ and Investigational Device Exemptions (IDEs) (21 CFR Part 812).¹¹ Of the regulations that provide special protections for vulnerable subjects found in Subparts B, C, and D of the DHHS regulations, FDA has promulgated regulations that provide protections for children (21 CFR Part 50, Subpart D 2001), comparable to Subpart D of the DHHS regulations, but FDA has not adopted Subparts B and C.

In exercising its oversight authority, FDA most frequently interacts with the sponsor of research, rather than with individual clinical investigators or IRBs. However, FDA does interact directly with clinical investigators and IRBs when conducting inspections and has the authority to impose sanctions against either of them for failing to satisfy regulatory requirements.

The Program for Good Clinical Practice (GCP) within the FDA commissioner's office serves as a focal point for FDA's human protection activities. The FDA GCP program:

program for good clinical practice

- coordinates FDA's human subjects protection policies;
- provides leadership and direction through the administration of FDA's Human Subjects Protection/ Good Clinical Practice Steering Committee;
- contributes to international GCP harmonization activities;
- plans and conducts training and outreach programs; and
- serves as a liaison with the Office for Human Research Protections (OHRP) and other federal agencies and external stakeholders committed to the protection of human research participants.

E. Differences Among FDA, DHHS, and Common Rule Regulations

The basic requirements of informed consent and IRB review are essentially the same between the FDA and the Common Rule regulations. However, there are some policies that are not universal and some differences in policy interpretation. First, most of the Common Rule departments and agencies have not adopted the additional DHHS protections for pregnant women, human fetuses, and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D). However, certain Common Rule agencies have administratively adopted one or more of the subparts, and these agencies sometimes have their own special requirements for protecting vulnerable populations.

In addition, some of the requirements of FDA regulations differ from those of the Common Rule. For example, FDA regulations hold the sponsors who submit the IND/IDE accountable whereas the Common Rule holds the funded institution accountable. Although almost identical in the basic requirements for informed consent and IRB review, there are differences based on FDA's statute and the nature of the research regulated by FDA, as shown in the following examples:

- The waiver of informed consent requirements for minimal risk research under §§____.116(c) and .116(d) of the Common Rule does not appear in FDA regulations, in large part because research involving medical products is rarely considered minimal risk research. And, the exception from informed consent requirements and the exemption from IRB review requirements found

⁸ See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm>.

⁹ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm?cfrpart=312>.

¹⁰ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm?cfrpart=600>.

¹¹ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm?cfrpart=812>.

in FDA regulations for emergency research (under 21 CFR 50.23 and 56.104, respectively) do not appear in the Common Rule. The Common Rule states that “nothing in this policy is intended to limit the authority of a physician to provide emergency medical care” (§_____.116(f)).

- The Common Rule exemptions at §101(b) for educational research; educational tests, surveys, interviews, and observations of public behavior; existing data documents, records, or specimens; and federal public benefit programs do not appear in FDA regulations, again,

because this type of research is generally not found in FDA’s regulations.

Reporting to the IRB of “unanticipated problems involving risks to subjects or others” is required under the Common Rule at §103(b)(5) and under FDA regulations at 21 CFR 56.108(b).

Table 3.2 provides a more comprehensive summary of the differences between the Common Rule regulations and those of FDA.

Table 3.2**Comparison of FDA Regulations and the Federal Policy for Human Subjects Protection**

FDA REGULATIONS	COMMON RULE
<p>56.101 Scope</p> <p>IRBs that review clinical investigations regulated by the FDA under §505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.</p>	<p>46.101 Scope</p> <p>All research involving human subjects conducted or supported by DHHS or conducted in an institution that agrees to assume responsibility for the research in accordance with 45 CFR 46, regardless of the source of funding.</p>
<p>56.102 and 50.3 Definitions</p> <p>Definitions for <i>act</i>; <i>application for research or marketing permit</i>; <i>emergency use</i>; <i>sponsor</i>; <i>sponsor-investigator</i>; <i>test article</i> do not have comparable terms defined in 45 CFR 46.</p> <p>FDA has defined <i>clinical investigation</i> to be synonymous with <i>research</i>. <i>Clinical investigation</i> means any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to FDA...or the results of which are intended to be later submitted to, or held for inspection by, FDA as part of an application for a research or marketing permit.</p> <p><i>Human subject</i> means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.</p> <p><i>Institutional Review Board</i> means any board, committee, or other group formally designated by an institution to review, to approve the initiation and to conduct periodic review of biomedical research involving human subjects. The primary purpose of such review is to ensure the protection of the rights and welfare of the human subjects. The term has the same meaning as the term <i>Institutional Review Committee</i> as used in §520(g) of the act.</p>	<p>46.102 Definitions</p> <p>Definitions for <i>department or agency head</i> and <i>certification</i> do not have comparable terms defined in 21 CFR 50 or 56.</p> <p>DHHS has defined research as a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalizable knowledge.</p> <p>DHHS has defined <i>research subject to regulation</i> and similar terms as intending to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, investigational new drug requirements administered by FDA).</p> <p><i>Human subject</i> means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.</p> <p><i>IRB</i> means an Institutional Review Board established in accordance with and for the purposes expressed in this policy.</p>

Definitions for IRB approval, minimal risk, institution, and legally authorized representative are identical.

<p>56.103 Circumstances that require IRB review</p> <p>Except as provided in 56.104 and 56.105, any clinical investigation that must meet the requirements for prior submission to FDA or considered in support of an application for a research or marketing permit must have been reviewed and approved by, and remained subject to continuing review by, an IRB meeting the requirements of this part.</p>	<p>46.103 Assuring compliance with this policy— research conducted or supported by any federal department or agency</p> <p>Sections dealing with assurances and certifications (a), (b)(1)-(3), (c)-(f) are unique to the Common Rule and the DHHS regulations.</p> <p style="text-align: right;"><i>(Continues on following page)</i></p>
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56.103 Circumstances that require IRB review (cont.)

[In diverging from the assurance requirement, FDA stated its belief that it is inappropriate for it to adopt the assurance mechanism. The benefits of assurance from IRBs that are subject to FDA jurisdiction, but not otherwise to DHHS jurisdiction, do not justify the increased administrative burdens that would result from an assurance system. FDA relies on its Bioresearch Monitoring Program, along with its educational efforts, to ensure compliance with these regulations.]

56.104 Exemptions from IRB requirement

- a. Any investigation that commenced before 7/27/81, and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before 7/27/81.
- b. Any investigation that commenced before 7/27/81 and was not otherwise subject to requirements for IRB review under FDA regulations before that date.
- c. Emergency use of a test article, provided that such emergency use is reported to the IRB within five working days. Any subsequent use of the test article at the institution is subject to IRB review.

46.101(b) Exemptions from this policy

- a. Research conducted in established or commonly accepted educational settings.
- b. Research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior.
- c. Research involving the use of educational tests (cognitive, diagnostic, aptitude achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b) of this section, if the human subjects are elected or appointed public officials or if these sources are publicly available.
- d. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- e. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and that are designed to study public benefit or service programs.
- f. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Identical Exemption:

Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe....

(Continues on following page)

<p>56.105 Waiver of IRB requirement</p> <p>On the application of a sponsor or sponsor-investigator, FDA may waive any of the requirements contained in these regulations, including the requirement for IRB review, for specific research activities, or for classes of research activities otherwise covered by these regulations.</p>	<p>No comparable provisions</p>
<p>56.107 and 46.107 IRB membership requirements are identical.</p>	
<p>56.108 and 46.108 “IRB functions and operations” are virtually identical, except 56.108 requires reporting to FDA.</p>	
<p>46.108 requires reporting to the department or agency head.</p>	
<p>56.109 and 46.109 “IRB review of research” are virtually identical with the following exceptions:</p> <ul style="list-style-type: none"> • 46.109(c) refers to the criteria in §_____.117 for waiving the requirement for a signed consent form §_____.117(c)(1) is not included in FDA’s regulations because FDA does not regulate research in which “the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality.” • 56.109(c) and (e) contain additional language related to FDA’s emergency research rule; DHHS published identical criteria for emergency research in a Secretarial announcement of waiver of the applicability of 45 CFR 46, 10/2/96. 	
<p>56.110 and 46.110 “Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research” are virtually identical except:</p> <ul style="list-style-type: none"> • 56.110 refers to the FDA, and 46.110 refers to the Secretary of DHHS or the department or agency head. • 56.110(d) states, “The FDA may restrict, suspend, or terminate an institution’s or IRB’s use of the expedited review procedure when necessary to protect the rights or welfare of subjects.” 46.110(d) states that, “The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution’s or IRB’s use of the expedited review procedures.” 	
<p>56.111 and 46.111 “Criteria for IRB approval of research” are virtually identical except 56.111 contains references to sections in Part 50, and 46.111 contains references to sections in Part 46.</p>	
<p>56.112 and 46.112 “Review by institution” are identical</p>	
<p>56.113 and 46.113 “Suspension or termination of IRB approval of research” are virtually identical, except 56.113 refers to FDA, and 46.113 refers to the department or agency head</p>	
<p>56.114 Cooperative research</p> <p>In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.</p>	<p>46.114 Cooperative research</p> <p>Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.</p>
<p>56.115 and 46.115 “IRB records” are virtually identical except:</p> <ul style="list-style-type: none"> • The list of IRB members required by 56.115(a)(5) is cross-referenced in 46.115(a)(5) to 46.103(b)(3). • 56.115(b) refers to FDA rather than the department or agency. • 56.115(c) states that, “The FDA may refuse to consider a clinical investigation if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.” Part 46 does not contain a comparable requirement. <p style="text-align: right;"><i>(Continues on following page)</i></p>	

56.120 Lesser administrative actions

The agency may:

- (1) withhold approval of new studies;
- (2) direct that no new subjects be added to ongoing studies;
- (3) terminate ongoing studies when doing so would not endanger the subjects;
- (4) when the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant state and federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB.

The parent institution is presumed to be responsible for the operation of an IRB, and FDA will ordinarily direct any administrative action against the institution. However, depending on the evidence of responsibility for deficiencies determined during the investigation, FDA may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

56.121 Disqualification of an IRB or an institution

The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

- (1) the IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part; and
- (2) the noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

56.122 Public disclosure of information regarding revocation

A determination that FDA has disqualified an institution and the administrative record regarding that determination are disclosable to the public under Part 20.

56.123 Reinstatement of an IRB or an institution

An IRB or an institution may be reinstated if the commissioner determines that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part.

56.124 Actions alternative or additional to disqualification

Disqualification of an IRB is independent of other proceedings or actions authorized by the act. FDA may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of or after disqualification. The agency may also refer pertinent matters to another federal, state, or local government agency for any action that that agency determines to be appropriate.

46.123 Early termination of research support; evaluation of applications and proposals

- (1) The department or agency head may require that support for any project be terminated or suspended when the department or agency head finds an institution has materially failed to comply with the terms of this policy.
- (2) In making decisions about supporting or approving applications or proposals the department or agency head may take into account factors such as whether the applicant has been subject to a termination or suspension under this section and whether the applicant or the person or persons who would direct or has directed the scientific and technical aspects of an activity has, in the judgment of the department materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a federal department or agency

The department or agency head will evaluate all applications and proposals involving human subjects. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

46.122 Use of federal funds

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

No comparable provisions

46.124 Conditions

With respect to any research project, the department head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

(Continues on following page)

50.20 and 46.116 General requirements for informed consent are virtually identical

50.25 and 46.116(a) Elements of informed consent are virtually identical, except:

- 50.25(a)(5) requires the confidentiality statement to note “the possibility that the FDA may inspect the records;”
- 46.116(c) and (d) state the conditions under which the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waive the requirement to obtain informed consent (the conditions could not apply in FDA-regulated research).

50.27 and 46.117 Documentation of informed consent are virtually identical, except:

- 46.117(c)(1) is not included in FDA’s comparative section contained in 56.109(c). 46.117(c)(1) allows the IRB to waive the requirement for the investigator to obtain a signed consent form if it finds that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality.

50.23(a)-(c) Exception from general requirements

Describes an exception from the general requirements for obtaining informed consent in circumstances that are life-threatening; informed consent cannot be obtained from the subject; time is not sufficient to obtain consent from the subject’s legal representative; and there is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the subject.

No comparable provisions

50.23(d) Waiver of informed consent for military personnel

Describes the criteria and standards that the President is to apply in making a determination that informed consent is not feasible or is contrary to the best interests of the individual in military exigencies in accordance with the Strom Thurmond Defense Authorization Act for FY 1999.

No comparable provisions

Notes:

- (1) *In 1991 FDA’s regulations were harmonized with the Common Rule to the extent permitted by statute.*
- (2) *Differences in the rules are due to differences in the statutory scope or requirements.*
- (3) *FDA has additional IRB requirements contained in parts 312, 812, and 814. For example, 812.2(b)(ii) states that research is considered to have an approved application for an IDE, unless FDA has notified the sponsor to the contrary, if IRB approval of the investigation is obtained after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk, and maintains such approval, and ensures informed consent is obtained in accordance with part 50.*
- (4) *DHHS has special subparts relating to vulnerable populations (for example, children, prisoners, and pregnant women). FDA has comparable provisions for children.*
- (5) *The Common Rule requires assurances and certifications from the grantee institution. FDA regulations generally require assurances of compliance from either or both the sponsor of the research and the clinical investigator.*

(Continues on following page)

F. Increased Interest in Human Research Protections

In the mid-1990s, public attention was again drawn to protections for human subjects with revelations about Cold War research at a variety of research institutions that un-

Advisory Committee on Human Radiation Experiments

knowingly exposed subjects to radiation. A presidential advisory committee, the Advisory Committee on Human Radiation Experiments, was established in January 1994 to investigate this research. It documented a number of abuses and called for reform of policies and practic-

es for all federal agencies that had signed onto the Common Rule, including the Department of Energy (ACHRE 1995). In February 1994, as a reminder to these agencies, President Clinton issued an executive memorandum ordering them “to cease immediately sponsoring or conducting any experiments involving humans that do not fully comply with the Federal Policy.”¹²

In the late 1990s, additional reports from the congressional U.S. General Accounting Office and the DHHS inspector general further stressed the need for significant improvements in federal mechanisms for protecting human subjects (DHHS OIG 2001; DHHS OIG 2000 a, b, c, d; DHHS OIG 1998 a, b, c, d, e).

Beginning in late 1998, OPRR became aware through site visits and incoming reports that certain institutions were not adhering to the regulatory requirements for IRB review of research, and it suspended authorizations for the conduct of research at a limited number of institutions. Over the next two

years, additional compliance actions were taken that resulted in the suspension of research at several large academic medical centers. These actions and highly publicized charges of widespread protocol deviations, regulatory violations, failures to report adverse events, and financial conflicts of interest raised public and professional awareness of human subjects protections issues.

In June 2000, the Secretary of DHHS elevated the human subjects protections functions of OPRR from its position within NIH to the office of Public Health and Science within the Office of the Secretary of DHHS. The reconstituted entity was named the Office for Human Research Protections (OHRP).

Office for Human Research Protections

Like its predecessor, OHRP has three statutory responsibilities.

These are to provide:

- education in the ethical conduct of human subjects research;
- compliance oversight of human subjects research supported by DHHS;
- administration of the institutional assurance process.

OHRP operates on the assumption that most research investigators and institutional administrators will take their responsibilities for protecting human subjects seriously once they fully understand them. Therefore, education is considered the key to responsible behavior and meaningful human subjects protection. However, along with its strong emphasis on education, OHRP continues to operate a strong compliance oversight program, asserting that research activities that ignore the rules and place subjects at risk are not tolerated.

¹² See <http://www.gpo.gov/fdsys/pkg/PPP-1994-book1/pdf/PPP-1994-book1-doc-pg281.pdf>.

Key Concepts:

The Regulatory Mandate to Protect Human Subjects

- Direct federal jurisdiction over the conduct of human subjects research extends only to research that is either
 - 1) conducted or supported by the federal departments and agencies that have adopted the Common Rule or
 - 2) regulated as research under a specific federal statute.
- There are currently three primary sources of federal regulatory protection for human research subjects:
 - 1) The Federal Policy (Common Rule) for the Protection of Human Subjects, codified or otherwise adopted by 16 executive branch departments and agencies, which is identical to Subpart A of 45 CFR Part 46;
 - 2) FDA Informed Consent and IRB regulations at 21 CFR Parts 50 and 56;
 - 3) DHHS regulations for the protection of human subjects, codified at 45 CFR Part 46, and including Subparts A through D.
- In 1953, the NIH Clinical Center introduced the mechanism of independent, group review to ensure protections for subjects, thus foreshadowing the modern IRB.
- In 1966, the U.S. PHS issued a PPO (#129) requiring review of grantees' clinical research by a committee of "institutional associates" who would ensure an independent determination of:
 - the rights and welfare of the subjects,
 - the appropriateness of the informed consent process, and
 - the risks and potential benefits of the investigation.
- DHEW in May of 1974 codified its human subjects protection policy as regulation at 45 CFR Part 46. Modifications to the DHHS regulations in 1981 resulted in regulations much like those currently in force. Subparts to the DHHS regulations provide additional protections for fetuses, pregnant women, and human in vitro fertilization (Subpart B 1975; revised as protections for pregnant women, human fetuses, and neonates in 2001), prisoners (Subpart C 1978), and children (Subpart D 1983).
- The 1981 recommendation for uniform federal human subjects regulations by the President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research was finally realized in 1991 with the promulgation of the Federal Policy for the Protection of Human Subjects (Common Rule) by 15 federal departments and agencies. One additional agency has adopted the Common Rule by statute or executive order.
- The Common Rule comprises Subpart A of the DHHS regulations at 45 CFR Part 46; 16 agencies are signatories to the rule.
- DHHS's OHRP enforces the DHHS human subjects protection regulations. All other agencies are also responsible for enforcing the regulations, although many defer to OHRP for the assurance process.
- FDA's human subjects protection regulations at 21 CFR Part 50 (for informed consent) and 21 CFR Part 56 (for IRB review) apply to clinical investigations that support applications for research or marketing permits for FDA-regulated products, including food and color additives, drugs, medical devices, and biological products for human use, and electronic products.
- Additional FDA regulations that are relevant to the protection of human subjects address INDs (21 CFR Part 312), Biological Products (21 CFR Part 600), IDEs (21 CFR Part 812), and Additional Protections for Children (21 CFR Part 50, Subpart D).

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Chapter 4

Education in Human Subjects Protection

- A. Introduction
- B. Need for Initial and Ongoing Education
- C. Elements of a Human Research Education Program
- D. Educational Approaches for Human Subjects Protections
- E. Responsible Conduct of Research
- F. Quality Improvement

Key Concepts

References



A. Introduction

This chapter outlines the knowledge base that is needed by those who play significant roles in reviewing, conducting, and supporting human subjects research (i.e., researchers, Institutional Review Board [IRB] members, IRB support personnel, and institutional officials). It also describes the elements needed for a successful human subjects protection education program and discusses emerging standards in the responsible conduct of research, including the incorporation of quality improvement measures.

The human subjects protection system in the United States ultimately depends on relationships of trust and responsibility among those who are involved in research. This is because no regulatory agency can inspect every clinical investigator or evaluate every IRB; no institution can audit every study; and no IRB can monitor every informed consent encounter. Those who volunteer to participate in research must have trust in the system, as must the public, which pays for much of the research and oversight.

Although it is not explicitly required by regulation, federal assurance offices (e.g., the Office of Human Research Protections [OHRP]; see Chapter 5) recommend that institutions and designated IRBs establish educational

training and oversight mechanisms to ensure that research investigators, IRB members and staff, and other appropriate personnel maintain continuing knowledge of relevant ethical principles. In addition, some funding agencies have a training requirement that applies to grantees (e.g., the National Institutes of Health [NIH]). Nonetheless, given the limited direct oversight that can be exercised in human subjects research, the system for protecting human research subjects depends on the integrity of each individual involved at every level of the research process. It is critical that each individual perform his/her role in a manner that safeguards the rights and welfare of every human research subject. This can be accomplished only if individuals are fully knowledgeable about their roles and responsibilities.

The need for ongoing education is highlighted by the constantly changing environment for human research—for example, issuance of new guidance by federal agencies, evolving science, and the changing cultural context in which research is conducted. Educational opportunities have to be timely, tailored to a group or a specific set of issues, and available in a diversity of formats that allow individuals to learn the information in a variety of ways, using various media.

B. Need for Initial and Ongoing Education

Research on human subjects is conducted by scientists from widely varying disciplines who are investigating a broad range of topics. Even within the biomedical sciences or the social and behavioral sciences, disciplines and topics of interest vary considerably.

The training received by scientists on ethical responsibilities and regulatory requirements for conducting human subjects research varies widely in quality, comprehensiveness, and content. Although they may be well trained regarding the research methods of their disciplines, scientists historically have received little theoretical or practical training about human subjects protection. The same can be said for research administrators and institutional officials at all levels.

Therefore, one of the responsibilities of an effective institutional human research protection program (HRPP) is to ensure that every individual has a basic understanding of the human protection responsibilities associated with his/her role.

Just as all professionals must keep abreast of developments within their research area, all who are involved in human subjects research must keep abreast of emerging concerns and requirements relative to the protection of human subjects in research, which is not a static activity but a dynamic one, based on developments in research, technology, and medicine. Theoretical debate is ongoing in the area of human subjects protections, and ethicists work to keep pace with new scientific developments. Practical issues emerge continually as new procedures, techniques, and interventions are introduced and new regulatory guidance is issued to keep pace with these changes.

Consequently, periodic ongoing education of research and administrative personnel is absolutely essential for ensuring continued high-level protections for human subjects. A strong HRPP will ensure that an organization's research personnel have up-to-date knowledge; otherwise, it risks the possibility that serious harm to human subjects and long-term damage to the viability of the organization's research enterprise might occur.

periodic ongoing education of research and administrative personnel

Researchers

The responsibility for person-to-person interactions with human research subjects and the day-to-day protection of

those subjects rest primarily with the researchers (i.e., with the Principal Investigator [PI], coinvestigators, study coordinators, and other members of the research team). As discussed in Chapter 1, the researchers are responsible for, among other things, implementing the research protocol correctly, obtaining legally effective informed consent, and maintaining meaningful lines of communication with research subjects.

As the individual responsible for every aspect of the research project, the PI holds ultimate responsibility for protecting the individuals who participate in the research. As the leader of the research team, it is critical for the PI to display both an appreciation of the importance of protecting human subjects and a detailed knowledge of the actual human subjects protection requirements. To the extent that any PI fails to appreciate or understand these requirements, other members of the research team can be expected to underestimate their importance as well.

Because every member of the research team is personally responsible for ensuring the rights and welfare of subjects, every member of the research team also must have an understanding of the basic ethical principles and regulatory requirements that govern human subjects research. In addition, individual members of the research team should possess detailed knowledge of the ethical concerns and regulatory requirements specific to his/her role in the research.

understanding of the basic ethical principles and regulatory requirements

For example, the individual whose role includes communicating directly with subjects during the informed consent process should have a detailed understanding of

- (1) the ethical issues related to the informed consent (e.g., the need to verify subjects' comprehension and capacity for consent);
- (2) the specific research protocol;
- (3) the regulatory requirements for obtaining and documenting informed consent.

Alternatively, individuals whose primary functions include maintaining case report forms and regulatory records need to have a detailed understanding of

- (1) the appropriate procedures for protecting privacy of subjects and maintaining confidentiality of study data;
 - (2) the specific research protocol;
 - (3) the federal regulatory record keeping requirements.
- Individuals who are involved in all of these activities must, of course, be well versed in all of the requirements described above.

Although it is not documented, it is reasonable to believe that most researchers continue to learn about human

subjects protection through on-the-job training. However, without an educational program to provide appropriate initial and continuing education, many will fail to gain a full understanding of their ethical and regulatory responsibilities for protecting human subjects and may inadvertently pay insufficient attention to critical issues.

IRB Members

As indicated in Chapter 1 and discussed in more detail in Chapter 8, IRB members are responsible for:

- (1) reviewing proposed research;
- (2) requiring prospective modifications in research to protect subjects' rights and welfare;
- (3) exercising continuing oversight from initiation to completion of the research.

To fulfill these responsibilities, IRB members must have a detailed knowledge of, among other things:

- (1) the ethical principles governing human subjects research;
- (2) the application of these ethical principles in practical settings;
- (3) the relevant regulatory requirements for the kinds of research they review; and
- (4) any special concerns related to the specific populations of subjects that will be involved in the research.

As the leaders of the IRB, the IRB chairperson and IRB administrator must demonstrate that they have detailed and up-to-date knowledge of the ethical concerns and regulatory requirements related to human subjects research. It is especially important for these individuals to ensure that the specific discussions and determinations required for the initial and continuing review of research take place and that these discussions and determinations are documented in accordance with regulatory requirements.

Most IRB members are volunteers, and relatively few of them have had specific professional training in the ethics and regulation of human subjects research prior to service on an IRB. Under these circumstances, initial and continuing education of IRB members constitutes a crucial element of any effective HRPP. IRBs whose chairperson and members lack a complete understanding of their ethical and regulatory responsibilities will inevitably fall short in their efforts to protect subjects—potentially resulting in physical, psychological, and/or social harm occurring to subjects and damage occurring to individual and institutional reputations.

IRB Administrator/Director and Staff

IRBs in most cases require both professional and clerical support (§____.103(b)(2)). The IRB administrator/

director should be an individual with professional-level training and experience. A background in ethics, law, or science is particularly beneficial, and specific training in the ethical principles and regulatory requirements for human subjects research is a necessity.

Clerical staff members also need to have a basic knowledge of human subjects protection standards, especially record-keeping standards, in order to fulfill their IRB duties. Moreover, clerical staff for smaller IRBs often serve as the only backup support for the professional IRB administrator/director. In such situations, it is particularly important that clerical staff receive initial and ongoing training in human subjects protection requirements.

Institutional Officials

It is the responsibility of institutional officials, especially the institutional human subjects signatory official (see Chapter 1), but including all officials having legal or oversight responsibility for human subjects protection, to ensure the development, implementation, and continued functioning of an effective institutional HRPP.

General knowledge about and appreciation for the ethical and regulatory responsibilities that accompany the conduct of human subjects research are essential prerequisites for all institutional officials, who, at every level, should inspire a culture of compliance, develop appropriate policies, and find the resources needed to support an effective HRPP.

Appropriate initial and ongoing education is necessary for institutional leaders to oversee HRPP functions effectively. Few institutional officials begin their jobs fully knowledgeable about human subjects protection issues, and still fewer can keep up with the evolving human subjects protection standards without a formal education program, especially with so many other responsibilities vying for their attention.

C. Elements of a Human Research Education Program

Elements of an Education Program

At a minimum, an education program for human research subjects protection should include the following subject matter:

- The modern history and evolution of human subjects protections.
- The ethical principles governing human subjects research.
- the requirements of federal and state law and regulations; and

Table 4.1 Basic Elements of a Human Research Education Program

Modern History of Human Subjects Protections

- Nazi atrocities
- Public Health Service (PHS) Syphilis Study at Tuskegee
- Studies identified by Henry Beecher (1966, 1959)
- Social and behavioral research on authority, conformity, and decisionmaking

Ethical Standards and Codes Relevant to Human Subjects Research

- The *Nuremberg Code* (Nuremberg 1949)
- The *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 2002)
- The *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (National Commission 1979)

Federal and State Law and Regulation

- The Federal Policy (Common Rule) for the Protection of Human Subjects¹
- Department of Health and Human Services (DHHS) regulations at 45 CFR Part 46, Subparts A, B, C, D²
- Food and Drug Administration (FDA) regulations at 21 CFR Part 50, Subparts A, B, and D, and Part 56³
- Federal agency-specific regulations and statutes
- State and local law on age of majority, emancipation, decisional competence, legally authorized representation, research protections (if any)

Institutional Policies and Procedures

- Institutional standards
- How to apply for IRB review
- Training in the completion of documents for IRB review

- institutional policies and procedures for the protection of human subjects.

Institutions should require that all researchers, IRB members, IRB staff members, and relevant institutional officials demonstrate basic knowledge in these four areas. Table 4.1 illustrates topics that each area might include.

Beyond this basic knowledge, identification of critical knowledge areas depends in part on the types of research typically conducted at the institution, on the subject population, and on the relative sophistication of the research community regarding human subjects protection issues.

Voluntary Versus Mandatory Educational Requirements

Recognizing the importance of protecting human research subjects, many institutions have implemented mandatory training requirements for investigators conducting human subjects research. Some institutions require that only PIs complete mandatory training and education related to

human subjects protection, while others extend the requirement to key personnel (the requirement when the research is supported by NIH),⁴ and still others extend the requirement to all individuals engaged in human subjects research activities.

The best practice is to require some level of knowledge about human subjects protection from all members of the research team. At some institutions, research personnel are required to attend a specific educational program, while other institutions require researchers to demonstrate competence by passing a test or earning a specified credential.

Documentation of Education

IRBs or institutions should maintain accurate records listing research investigators, IRB members, IRB staff, and research staff who have fulfilled the institution's human subjects protection knowledge requirements. Such records should be available for review by the human subjects

¹ See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

² See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

³ See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html and www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html.

⁴ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html> and http://grants.nih.gov/grants/policy/hs_educ_faq.htm.

signatory official or by others as a part of compliance monitoring activities.

Continuing Education

Although there is general agreement that continuing education in human subjects research protection issues is needed, no widely accepted standards have been developed concerning the nature or frequency of this training. A few institutions require annual training of some sort, but among those requiring mandatory continuing education, with a few exceptions, updating at two- to three-year intervals currently appears to be the most common approach.

D. Educational Approaches for Human Subjects Protection

There are a number of tools available for providing basic human subjects protection education, including live didactic training, books, other printed materials, and computer-based tutorials and modules. Some are publicly available, while others are available commercially. Examples of such tools are provided in Table 4.2.

Of course, the choice of appropriate educational approaches and materials depends on the needs of both the institution and the individuals involved in the conduct and

oversight of research. However, many institutions opt to provide several different mechanisms for learning (textbooks, computer modules, live training) so that investigators, IRB members and staff, and appropriate institutional officials can gain the basic information needed to conduct, administer, or oversee human research.

It is important to recognize that different people have different ways of learning most effectively. Some, for example, learn best through a lecture format, while others benefit most from discussion and analysis and/or discussion of case studies. Some learn better in groups, while others do best on their own. Some feel comfortable with computer-assisted instruction, while others prefer to learn through different modes.

As a result, a variety of mechanisms should be made available through which researchers, IRB members and staff, and appropriate institutional officials can acquire and demonstrate the basic knowledge needed to protect human subjects involved in the research that they conduct or oversee. In addition, courses and/or discussion sessions that are offered need to be presented at convenient times for all who need training and education.

a variety of mechanisms should be made available

Table 4.2
Examples of Education Resources for Human Subjects Protection

Basic Education

- Dunn and Chadwick, *Protecting Study Volunteers in Research, 2nd Edition* (2002)
- CITI Human Subjects Research Educational Program (Web-based modules)⁵
- OHRP Training Modules⁶
- OHRP *Guidance by Topic*⁷
- National Science Foundation Division of Grants and Agreements, *Interpreting the Common Rule for the Protection of Human Subjects for Behavioral and Social Science Research*⁸
- Food and Drug Administration Information Sheets
- OHRP *Public Responsibility in Medicine and Research (PRIMR) Investigator 101* (CD-ROM)

Education for IRB Members and IRB Staff

- Amdur and Bankert, *Institutional Review Board Management and Function* (2002)
- Russell-Einhorn and Puglisi, *Institutional Review Board Reference Book* (2001)
- *IRB: A Review of Human Subjects Research* (scientific journal), the Hastings Center, Garrison, NY
- IRB Forum⁹
- OHRP *Common Compliance Findings and Guidance*¹⁰

⁵ See http://jaguar.ir.miami.edu/~citireg/citi_information.html.

⁶ See www.hhs.gov/ohrp/education/.

⁷ See <http://www.hhs.gov/ohrp/policy/>.

⁸ See <http://www.nsf.gov/bfa/dias/policy/hsfaqs.jsp>.

⁹ See www.irbforum.com/.

¹⁰ See www.hhs.gov/ohrp/compliance/.

Resources for Researchers

Textbooks and computer-based training modules should be chosen based on the relevance of content and ease of access. Many of the free, Web-based training modules are designed for specific types of research (i.e., oncology research, research conducted by NIH) and are less useful for researchers in unrelated areas, such as behavioral and social sciences research.

Investigators and study coordinators can particularly benefit from the smaller, local and regional human subjects protection events sponsored by OHRP that are now occurring with increasing frequency around the country.

IRB Members and Staff

IRB members and staff should be required to complete the same ethics training that is required of researchers so that they become familiar with its content. In addition, IRB members need specialized training in human subjects protection regulations (i.e., criteria for approval of research; criteria for waiver of informed consent, criteria for waiver of documentation of consent, and criteria for involvement of children, prisoners, pregnant women, human fetuses, or neonates in research). The development of reviewer checklists can help IRB members and staff learn and apply these criteria appropriately.

Continuing education of IRB members also is an important matter. To do their jobs well, IRB members must be aware of developing controversies and new regulatory guidance.

In addition to the knowledge required by IRB members, IRB staff members need particular education in certain requirements of human subjects regulations. They need to

continuing education of IRB members

be trained to take meaningful minutes of IRB meetings that capture the substance of the discussion without providing unnecessary detail. They also

need to learn how to document required IRB determinations, track protocol changes and reports that involve unanticipated problems that involve risks to subjects or others, as well as adverse events, and maintain accurate and complete IRB records for the life of the research. They must also know that those records must be maintained for three years after the research ends.

Attending regular meetings (such as those sponsored by PRIMR, the Applied Research Ethics National Association,

as well as the Department of Health and Human Services (DHHS), OHRP, Food and Drug Administration (FDA), and other Common Rule agencies has become a necessity for IRB chairpersons and professional staff. IRB members also benefit from attending these meetings, as well as the smaller, local and regional human subjects protection events referenced above.

As mentioned in Chapter 1, IRB staff must have a detailed, working knowledge of all relevant regulatory requirements. Certification as an IRB professional increasingly is becoming a standard expectation of employers seeking IRB professional staff.¹¹ A number of organizations offer such certification programs.

Institutional Officials

As indicated previously, any officials with institutional responsibilities for protecting human subjects need to have a basic understanding of the ethical principles and regulatory requirements relating to human subjects research. At an absolute minimum, these officials must be familiar with the responsibilities outlined in the training module for institutional officials that is located on the OHRP Web site.¹²

E. Responsible Conduct of Research

In addition to specific knowledge about human subjects protection requirements, the responsible conduct of research also requires knowledge about professional standards in a variety of areas affecting the way research is conducted. For example, professional standards relating to (1) data acquisition, management, sharing, and ownership; (2) mentor-trainee relationships and responsibilities; (3) publication practices and authorship; (4) peer review; (5) scientific collaboration; (6) animal welfare; (7) conflict of interest and commitment; (8) good clinical, laboratory, and manufacturing practices; and (9) research misconduct all have been suggested as integral to the ethical and responsible conduct of research.

As a result, many institutions have begun to provide researchers with educational opportunities and materials in one or more of these areas. Some institutions have implemented full programs in the responsible conduct of research that cover all of the areas referenced above.

This section provides a brief introduction to two areas relevant to the ethical conduct of research: research misconduct and conflict of interest.

¹¹ See www.primr.org/certification/overview.html; www.naim.org/.

¹² See www.hhs.gov/ohrp/.

Research Misconduct

The 1985 Health Research Extension Act requires institutions seeking federal research grants to establish “an administrative process to review reports of scientific fraud” and to “report to the Secretary [DHHS] any investigation of alleged scientific fraud, which appears substantial” (see Table 4.3).¹³

Regulatory procedures for dealing with scientific misconduct were established in 1989 (42 CFR Part 50, Subpart A) - now 42 CFR Part 93 - and, for Public Health Service funded research, are overseen by the DHHS Office of Research Integrity (ORI). Other agencies have similar research misconduct policies. Research misconduct (42 CFR 93.102) is defined in the regulations as fabrication, falsification, or plagiarism, in proposing, performing, or reviewing research, or in reporting research results. Research misconduct does not include honest error or differences of opinion.

Although there is general agreement that institutions should provide training to researchers relative to the responsible conduct of research, current regulations and guidance do not stipulate the form or content for this training. However, model policies can be found at several federal agencies.¹⁴

DHHS Office of Research Integrity

Subpart A) - now 42 CFR Part 93 - and, for Public Health Service funded research, are overseen by the DHHS Office of Research

Integrity (ORI). Other agencies have similar research misconduct policies. Research misconduct (42 CFR 93.102) is defined in the regulations as fabrication, falsification, or plagiarism, in proposing, performing, or reviewing research, or in reporting research results. Research misconduct does not include honest error or differences of opinion.

Avoidance of Conflict of Interest

“Conflict of interest” can be defined as any situation in which financial, professional, or personal obligations may compromise or present the appearance of compromising an individual’s professional judgment in designing, conducting, analyzing, or reporting research (see Chapter 22 for more detailed discussion about this issue). All staff of an HRPP should be educated about the regulatory requirements for disclosing and managing conflicts of interest.

The Public Health Service (PHS) regulations at 42 CFR Part 50, Subpart F, address how *institutions* receiving PHS support (i.e., from NIH, the Centers for Disease Control and Prevention, the Indian Health Service) should handle financial conflict of interest. Institutions receiving support from National Science Foundation (NSF) must meet identical requirements.¹⁵ The PHS regulations require that institutions establish policies and procedures relating to the disclosure and management of financial conflicts of interest for researchers, their spouses, and their dependent children. Once a significant financial interest has been disclosed by a researcher, it is up to the institutional conflict of interest official (or conflict of interest committee) to determine whether the disclosed financial interest requires management. The IRB should be notified of any conflict affecting personnel involved in human subjects research.

PHS regulations on financial conflict of interest

Table 4.3

Institutional Responsibilities Regarding Allegations of Research Misconduct

Public Health Service responsible conduct of research regulations at 42 CFR Part 50, Subpart A, require that the institution:

- launch an inquiry immediately upon receiving an allegation;
- complete the inquiry within 60 days, determine if an investigation is warranted, and document that determination;
- where an investigation is warranted, notify Office of Research Integrity of its initiation, progress, and outcome;
- afford confidentiality protections for those who report possible misconduct and those who are affected by inquiries and investigations;
- undertake diligent efforts to restore the reputations of persons alleged to have engaged in misconduct when allegations are not confirmed;
- undertake diligent efforts to protect the positions and reputations of those persons who make allegations in good faith;
- where warranted, conduct a thorough and authoritative investigation to include:
 - document examination,
 - interviews with all relevant parties,
 - consultation with appropriate experts,
 - precautions against real or apparent conflicts of interest on the part of those taking part in the inquiry or investigation, and
 - documentation sufficient to substantiate the investigation’s findings;
- impose appropriate sanctions where misconduct has been substantiated.

¹³ See <http://grants1.nih.gov/grants/olaw/references/hrea1985.htm>.

¹⁴ See, for example, the ORI’s policy at <http://ori.dhhs.gov/misconduct/>.

¹⁵ See www.nsf.gov/oig/coi.pdf.

Any proposed management plan must be determined by the IRB to be satisfactory from a human subjects protection perspective.

FDA regulations at 21 CFR Part 54 govern individual investigator disclosure of financial conflicts of interest to sponsors of FDA-regulated research. These regulations require that investigators disclose information related to conflicts of interest for themselves, their spouses, and their dependent children to the research sponsor so that the sponsor can inform FDA. Most institutions require investigators to provide copies of all disclosures provided to sponsors to the conflict of interest official or committee.

F. Quality Improvement

In recent years, there has been growing emphasis on a proactive and interactive system of human subjects protection, rather than a reactive, compliance-focused system of oversight and sanctions. Continuous quality improvement (CQI) is a critical means for ensuring that specific functions are being implemented and goals met in an HRPP. In addition, the process of CQI serves an educational goal in that it forces organizations to revisit roles and responsibilities continuously. CQI programs can increase the quality, performance, and efficiency of an HRPP through a self-assessment process followed by the setting of new standards and benchmarks for institutional improvement.

Several federal offices and agencies (e.g., OHRP, Office of Veterans Affairs) have developed self-assessment tools and programs that institutions can use to establish baseline measures against which they can assess their progress.

Key Concepts: Education in Human Subjects Protection

- An effective institutional HRPP must ensure that every individual involved in the conduct or oversight of human subjects research has a basic understanding of the human protection responsibilities associated with his/her research role.
- Ethically, the PI holds ultimate responsibility for the protection of the human subjects participating in the research. Under the Common Rule, this responsibility is borne by the institution, which, in turn, may delegate operational responsibility to the IRB.
- Because every member of the research team is personally responsible for ensuring the rights and welfare of subjects, every member of the research team should have an appropriate understanding of the basic ethical principles and regulatory requirements that govern human subjects research.
- Individual members of the research team also should possess detailed knowledge of the ethical concerns and regulatory requirements specific to his/her role in the research.
- IRB members must have a detailed knowledge of (1) the ethical principles governing human subjects research, (2) the application of these ethical principles in practical settings, (3) the relevant regulatory requirements for the kinds of research they review, and (4) any special concerns related to the specific populations of subjects that will be involved in the research.
- IRB members need specialized training in how to conduct a structured review of research that addresses all the criteria contained in the human subjects protection regulations.
- The IRB administrator/director should be an individual with training and experience at the professional level. A background in ethics, law, or science is particularly helpful, and specific training in the ethical principles and regulatory requirements for human subjects in research is essential.
- IRB staff members must be educated in the documentation requirements of the human subjects regulations.
- Knowledge about and appreciation for the ethical and regulatory responsibilities that accompany the conduct of human subjects research are essential prerequisites for institutional officials.
- At a minimum, an education program for human subjects research protection should include (1) the modern history and evolution of human subjects protections, (2) the ethical principles governing human subjects research, (3) the requirements of federal and state law and regulations, and (4) institutional policies and procedures for the protection of human subjects.
- Institutions seeking federal research grants are required to establish “an administrative process to review reports of scientific fraud” and “report to the Secretary [DHHS] any investigation of alleged scientific fraud which appears substantial.”
- Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
- “Conflict of interest” can be defined as any situation in which financial, professional, or personal obligations may compromise or present the appearance of compromising an individual’s professional judgment in designing, conducting, analyzing, or reporting research. PHS regulations address how institutions receiving PHS or NSF support should handle financial conflict of interest. FDA regulations govern individual investigator disclosure of financial conflicts of interest to sponsors of FDA-regulated research. The HRPP is responsible for ensuring that all relevant parties are educated in the requirements for disclosing and managing conflicts of interest.
- CQI is a process that can both improve the system of protections within an institution and also serve an educational function as individuals and offices within the institution are forced to assess their policies and programs against a set of goals and/or measures.

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Chapter 5

Institutional Review Board Registration and Assurances of Compliance

- A. Introduction
 - B. Institutional Review Board Registration
 - C. Basic Office for Human Research Protections Assurance Application Requirements
 - D. Terms of the Federalwide Assurance for Institutions Within the United States
 - E. Terms of the Federalwide Assurance for International (Non-U.S.) Institutions
 - F. Status of Existing Assurances
- Key Concepts**
References



A. Introduction

Assurances of compliance (referred to as *assurances*) with federal regulations for the protection of human subjects were first developed in the late 1960s, when the National Institutes of Health put into practice a policy for implementing the federal requirements at grantee institutions. Assurances were negotiated with each institutional grantee, allowing each institution to create its own policies and procedures for protection as long as they were fully consistent with federal regulations. The negotiation process also allowed federal officials to educate institutions about requirements and procedures for protecting human subjects in research. Because the assurance indicated what an institution intended to do to protect research subjects, it served essentially as a pledge or commitment on behalf of an institution to comply with all appropriate regulations and guidance.

In the late 1970s, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral

**uniform
implementation of
the federal
regulations**

Research (National Commission) determined that there should be uniform implementation of the federal regulations and recommended that each

institution engaged in regulated research should provide assurance to a single federal office that all research would be conducted in accordance with federal regulations (National Commission 1978). This perspective was reinforced by the President's Commission for the Study of Ethical Problems in Biomedical and Behavioral Research (the President's Commission), which outlined further steps for ensuring the coordination of federal monitoring in order to minimize the bureaucratic burden imposed on institutions (President's Commission 1983).

A single office was never created, however. Instead, it was determined that each federal department and agency could issue its own assurance, although many now rely on the assurance process provided by the Department of Health and Human Services (DHHS) (currently through its Office for Human Research Protections [OHRP], as described below). Institutions must provide this assurance as a condition of receiving federal funds for research from agencies that are signatories to the Federal Policy for the Protection of Human Subjects (also known as the Common Rule). For the most part, the negotiation process for assurances has developed into a routine procedure through which standardized documents that mirror the federal regulations may substitute for independently negotiated assurances specific to the institution's culture, policy, and procedures.

OHRP revised the assurance process effective December 2000 and is currently testing the new procedures.¹ The revised process, which was approved by the Office of Management and Budget in February 2005, calls for the use of one Federalwide Assurance (FWA) document for domestic institutions and another assurance document for foreign institutions. Each legally separate institution must obtain its own FWA, and assurances approved under this process cover all of the institution's federally supported research involving human subjects.

Although at this time OHRP continues to honor existing assurance options until they must be renewed—the FWA, the Multiple Project Assurance (MPA), the Cooperative Project Assurance (CPA), and the Single Project Assurance (SPA)—under the new policy, the FWA will replace MPAs, SPAs, and CPAs.² OHRP encourages institutions that need an OHRP-approved assurance to submit an FWA because it is the simplest type of assurance to complete (new FWA submissions may be completed electronically or on paper) and because it applies broadly to all human subjects research

Federalwide Assurance (FWA)

conducted or supported by DHHS, as well as to human subjects research conducted or supported by most other U.S.

federal departments and agencies. Federal agencies can still choose whether to use the new assurance process or issue their own.

The new assurance process is intended to reduce the burden on institutions by allowing them to qualify for one FWA that may be renewed every three years. It should be noted that, although the content of the new assurance document is similar to that of previous assurance documents, additional requirements are provided that institutions must meet, such as institutional staff completing OHRP's computerized educational training.

Obtaining an approved assurance from OHRP is a two-step process. First, an assurance application cannot be submitted until an institution ensures that the Institutional Review Board (IRB) to be designated under the assurance is registered with OHRP. Second, registration of IRBs is

required, whether or not they review research sponsored or regulated by a federal agency that follows the Common Rule.

This chapter describes the OHRP IRB registration process and the subsequent process for negotiating an assurance of compliance. Actions that OHRP can take if an institution violates an assurance are described in Chapter 6 of this manual.

Although the Food and Drug Administration (FDA) does not require its sponsors to provide assurances of compliance, it does require investigators to provide a written commitment that, before initiating an investigation subject to an institutional review requirement under 21 CFR 56, an IRB will review and approve the investigation in accordance with 21 CFR 56 [21 CFR 312.53(c)(1)(vi)(d); 312.53(c)(1)(vii); 21 CFR 812.43(c)(4)(i)]. The sponsor makes similar commitments (21 CFR 312.23(a)(1)(iv); 21 CFR 812.20(b)(6)).

B. IRB Registration³

Only institutions or organizations that operate their own IRBs or Independent Ethics Committees (IECs) should submit an IRB/IEC registration form.³ Institutions that do not operate their own IRB/IECs but rely on the IRB/IEC of another institution should not submit an IRB registration. The goal of the registration system is to facilitate OHRP's efforts to establish effective communications with IRB/IECs working to protect human subjects, especially those responsible for DHHS-regulated or DHHS-supported research. Currently, registration is required only for IRB/IECs designated under an OHRP FWA. However, other IRB/IECs are encouraged to register voluntarily. IRB registration currently is not required by FDA.

registration is required only for IRB/IECs designated under an OHRP FWA

The following information is requested on the registration application:

- the name of the organization operating the IRB/IEC;
- the senior or head official of the organization operating the IRB/IEC;

¹ The assurance process described in this document is that used by the OHRP. Investigators conducting research funded by non-DHHS agencies should check with their funding agency regarding its assurance process.

² Under the guidelines of the previous system, institutions with an MPA were independently responsible for approving new human subjects research projects. That is, once an Institutional Review Board approves a project, it may begin. In contrast, institutions with an SPA had to seek approval from the agency holding the assurance prior to the initiation of every project.

³ On July 7, 2004, OHRP proposed requiring the registration of IRBs that review human subjects research that is conducted or supported by DHHS and that is designated under an assurance of compliance approved for federalwide use by OHRP. Under the current OHRP IRB registration system, the submission of certain information is required by the existing DHHS human subjects protection regulations, and certain other information may be submitted voluntarily. Under the proposed rule, all registration information will be required, making the IRB registration system uniform with the proposed IRB registration requirements of the FDA and creating a single DHHS IRB registration system. FDA simultaneously published a proposed rule regarding FDA IRB registration requirements.

- the person providing this information
- Information on each IRB/IEC to be registered, updated, or renewed (e.g., behavioral, biomedical)
- the city and state or country for each IRB/IEC, if different from the organizational location
- accreditation status of the IRB or its parent organization by a human subjects protection accrediting organization, and the name of accrediting organization
- the approximate total number of currently active protocols
- the approximate number of full-time positions devoted to the IRB's administrative activities
- information regarding whether the IRB reviews or intends to review (within the three-year period covered by the IRB registration) research supported by the U.S. government
- the approximate number of currently active protocols supported by DHHS
- the approximate number of currently active protocols supported by other federal departments and agencies
- information regarding whether the IRB reviews or intends to review (e.g., within the three-year period covered by the IRB registration) research that is regulated by FDA
- the approximate number of currently active protocols involving products regulated by FDA
- the categories of products that are studied in active FDA-regulated protocols that are reviewed by the IRB
- the name and title of the IRB/IEC chairperson
- the IRB roster with relevant information (to ensure that it meets the minimum requirements for membership) as follows:
 - name,
 - gender,
 - highest degree earned,
 - primary scientific or nonscientific specialty,
 - affiliation with institution(s), and
 - alternate members (see Chapter 7)

OHRP will contact the applicant institution if there are any questions about the registration. Once an institution has submitted an IRB/IEC registration, it can track the progress of the document on OHRP's Web site until the IRB/IEC is registered. Once an institution's IRB/IEC registration has been processed, it will be listed on the OHRP Web site.⁴

C. Basic OHRP Assurance Application Requirements

If an institution is engaged in human subjects research (not otherwise exempt) that is conducted or supported by any agency of DHHS, it must have an OHRP-approved assurance of compliance with the DHHS regulations (§____.103) for the protection of human subjects. The requirement to file an assurance includes both awardee and collaborating performance-site institutions.

Under the Common Rule at §____.102(f) awardees and their collaborating institutions become engaged in human subjects research whenever their employees or agents: (1) intervene or interact with living individuals for research purposes or (2) obtain, release, or access individually identifiable private information for research purposes. In addition, awardee institutions are automatically considered to be engaged in human subjects research whenever they receive a direct DHHS or other Common Rule signatory agency award to support such research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award. The awardee also is responsible for ensuring that all collaborating institutions engaged in the research hold an approved assurance prior to their initiation of the research.

Common Rule definition of "engaged" in human subjects research

If the research is conducted or supported by a non-DHHS agency that is also a signatory to the Common Rule, a written assurance must be on file with the funding agency or with DHHS, whichever agency has been designated. Thus, in lieu of requiring submission of an assurance, individual department or agency heads can accept the existence of a current assurance, appropriate for the research in question, on file with OHRP and approved for federalwide use by that office. When the existence of a DHHS-approved assurance is accepted in lieu of requiring the submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads also should be made to OHRP.

The FWA, Terms of Assurance (see page 5-4), and IRB registration may be relied upon by other federal departments and agencies. However, if an institution does not receive any DHHS support and does not have an assurance on file with OHRP, the institution may be required to file an assurance of compliance with the federal department or agency supporting the research, as specified by that department or agency.

⁴ See <http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>.

In essence, the assurance states that the institution will conduct its human subjects research in accordance with the regulations. Assurances applicable to federally supported or conducted research at a minimum include the following:

- A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This could include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under the Common Rule at §___101.(b) or (i).
- Designation of one or more IRBs established in accordance with the requirements set forth in the regulations and for which provisions are made for meeting space and sufficient staff to support the IRB's review and record-keeping duties.
- A list of IRB members identified by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution. Changes in IRB membership should be reported to the department or agency head, unless the existence of a DHHS-approved assurance is accepted. In this case, a change in IRB membership should be reported to OHRP.
- Written procedures to be followed by the IRB include those
 - for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
 - for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and
 - for ensuring prompt reporting to the IRB of proposed changes in a research activity and for ensuring that such changes in approved research, during the period for which IRB approval already has been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.
 - Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of any unanticipated

problems that involve risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB as well as any suspension or termination of IRB approval.

The assurance should be submitted and executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the regulations. The department or agency head (or OHRP) evaluates all assurances submitted, taking into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

On the basis of this evaluation, OHRP or the department or agency head may approve or disapprove the assurance or enter into negotiations to develop an approvable one. The department or agency head can limit the period during which any particular approved assurance or class of approved assurances should remain effective or can otherwise condition or restrict approval.

Subsequently, an institution with an approved assurance must certify that each application or proposal for research covered by the assurance has been reviewed and approved by the IRB covered by the assurance. Such certification must be submitted with the application or proposal. Under no condition should research covered by the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research should certify within 30 days after the receipt of a request for such a certification from the department or agency that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

D. Terms of the FWA for Institutions Within the United States

The terms of the assurance agreement negotiated by OHRP are described in the following paragraphs. Individual agencies might include additional terms and conditions for granting an assurance.

Human Subjects Research Must Be Guided by Ethical Principles

All of the institution's human subjects activities and all activities of the IRBs designated under the assurance,

regardless of funding source, will be guided by the ethical principles in:

- the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (*Belmont Report*) of the National Commission (1979) for the Protection of Human Subjects of Biomedical and Behavioral Research;
- other appropriate ethical standards recognized by federal departments and agencies that have adopted the Common Rule.

Applicability

These terms apply whenever the institution becomes engaged in federally supported (i.e., conducted or supported) human subjects research that is not otherwise exempt from the Common Rule. The institution becomes so engaged whenever:

- the institution's employees or agents intervene or interact with human subjects for purposes of federally supported research;
- the institution's employees or agents obtain individually identifiable private information about human subjects for purposes of federally supported research; or
- the institution receives a direct federal award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator.

Compliance with the Common Rule

Institutions conducting federally supported human subjects research and the IRB(s) designated under the institution's assurance will comply with the Common Rule at Subpart A. All federally supported human subjects research also will comply with any additional human subjects regulations and policies of the supporting department or agency. All human subjects research conducted or supported by DHHS will comply with all subparts (A, B, C, and D) of the DHHS regulations at Title 45 CFR Part 46.

Written Procedures Required by OHRP

The institution should establish, and should provide a copy to OHRP upon request, written procedures for:

- ensuring prompt reporting to the IRB, appropriate institutional officials, the relevant department or agency head, any applicable regulatory body, and OHRP of any
 - unanticipated problems involving risks to subjects or others,
 - serious or continuing noncompliance with the federal regulations or IRB requirements, and
 - suspension or termination of IRB approval,

- verifying, by a qualified person or persons other than the investigator or research team, whether proposed human subjects research activities qualify for exemption from the requirements of the Common Rule.

The designated IRB has established, and will provide a copy to OHRP upon request, written procedures for:

- conducting IRB initial and continuing review (not less than once per year), approving research, and reporting IRB findings to the investigator and the institution; and
- determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review; and
- ensuring that changes in approved research protocols are reported promptly and are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject.

Responsibilities and Scope of IRBs

Except for research exempted or waived in accordance with §101(b) or §101(i) of the Common Rule, all human subjects research will be reviewed and prospectively approved and will be subject to continuing oversight and review at least annually by the designated IRB. The IRB will have the authority to approve, require modifications in, or disapprove the covered human subjects research.

all human subjects research reviewed and prospectively approved

Informed Consent Requirements

Except for research exempted or waived in accordance with §101(b) or §101(i) of the Common Rule, informed consent will be

- sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by §116 of the Common Rule; and
- appropriately documented in accordance with and to the extent required by §117 of the Common Rule.

Requirement for Assurances for Collaborating Institutions/Investigators

The institution is responsible for ensuring that all institutions and investigators engaged in its federally supported human subjects research operate under an appropriate OHRP or other federally approved assurance for the protection of human subjects. In some cases, one

institution may operate under an assurance issued to another institution with the approval of the supporting department or agency and the institution holding the assurance.

Written Agreements with Nonaffiliated Investigators

The engagement in human research activities of each independent investigator who is not an employee or agent of the institution may be covered under an FWA only in accordance with a formal, written agreement of commitment to relevant human subjects protection policies and IRB oversight. OHRP's sample Unaffiliated Investigator Agreement may be used or adapted for this purpose, or the institution may develop its own commitment agreement. Institutions must maintain commitment agreements on file and provide copies to OHRP upon request.

Institutional Support for IRBs

The institution will provide assurance to the IRB that it operates with resources and professional and support staff sufficient to carry out its responsibilities under the assurance effectively.

Compliance with the Terms of Assurance

The institution accepts and will follow the terms listed above and is responsible for ensuring that:

- the IRB designated under the assurance agrees to comply with these terms;
- the IRB possesses appropriate knowledge of the local research context for all research covered under the assurance.

Any designation under this assurance of another institution's IRB or an independent IRB must be documented by a written agreement between the institution and the IRB organization that outlines their relationship and includes a

IRB authorization agreement

commitment that the designated IRB will adhere to the requirements of this assurance.

OHRP's sample IRB Authorization Agreement may be used for this purpose, or the two organizations may develop their own agreement. This agreement should be kept on file at both organizations and made available to OHRP upon request.

Assurance Training

The OHRP Assurance Training Modules describe the major responsibilities of the Institutional Signatory Official, Human Protection Administrator, and IRB Chairperson that must be fulfilled under the assurance. Agencies and depart-

ments strongly recommend that the Institutional Signatory Official, the Human Protections Administrator (e.g., Human Subjects Administrator or Human Subjects Contact Person), and IRB chairperson personally complete the relevant OHRP Assurance Training Modules or comparable training that includes the content of these modules prior to submitting an assurance.

Educational Training

OHRP strongly recommends that the institution and the designated IRB establish educational training and oversight mechanisms (appropriate to the nature and volume of its research) to ensure that research investigators, IRB members and staff, and other appropriate personnel maintain continued knowledge of and compliance with relevant ethical principles, relevant federal regulations, OHRP guidance, other applicable guidance, state and local laws, and institutional policies for the protection of human subjects. Furthermore, OHRP recommends that IRB members and staff complete relevant educational training before reviewing human subjects research and research investigators complete appropriate educational training before conducting human subjects research.

OHRP Assurance Training Modules

Renewal of Assurance

All information provided under the assurance must be updated at least every 36 months (three years), even if no changes have occurred, in order to remain active. Failure to update this information could result in restriction, suspension, or termination of the institution's FWA for the protection of human subjects.

E. Terms of the FWA for International (Non-U.S.) Institutions

Human Subjects Research Must Be Guided by Ethical Principles

All of the institution's human subjects activities and all activities of the IRBs or IECs designated under the assurance, regardless of funding source, will be guided by one of the following statements of ethical principles:

- The World Medical Association's *Declaration of Helsinki* (as adopted in 1996 or 2000)
- The *Belmont Report*
- Other appropriate international ethical standards recognized by federal departments and agencies that have adopted the Common Rule

Applicability

These terms apply whenever the institution becomes engaged in U.S. federally supported human subjects research that is not otherwise exempt from the Common Rule, as described above in the terms for U.S. institutions. If a U.S. department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided by the U.S. Common Rule, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided above, consistent with the requirements of §101(h) of the Common Rule.

Compliance with Regulations, Policies, or Guidelines

All U.S. human subjects research supported by a federal agency that implements the Common Rule must comply with the requirements of any applicable U.S. federal regulatory agency as well as one or more of the following:

- the Common Rule (e.g., Subpart A) or the U.S. DHHS regulations at 45 CFR 46 and its Subparts A, B, C, and D⁵
- the May 1, 1996, International Conference on Harmonisation *E-6 Good Clinical Practice: Consolidated Guidance* (ICH-GCP-E6), sections 1 through 4
- the 2002 Council for International Organizations of Medical Sciences *International Ethical Guidelines for Biomedical Research Involving Human Subjects*
- the 1998 Medical Research Council of Canada *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*
- the 2000 Indian Council of Medical Research *Ethical Guidelines on Biomedical Research Involving Human Subjects*
- other standards for the protection of human subjects recognized by U.S. federal departments and agencies that have adopted the U.S. Common Rule

All other requirements are the same as for U.S. institutions (described above). The terms for non-U.S. institutions differ only in a category called “Considerations for Special Class of Subjects.” These terms require that, for DHHS-supported human subjects research, the institution will comply with 45 CFR 46 Subparts B, C, and D prior to the involvement of pregnant women or fetuses, prisoners, or children, respectively. For non-DHHS U.S. federally supported human subjects research, the institution will comply with any human subjects regulations and/or policies of the supporting department or agency for these classes of subjects.

F. Status of Existing Assurances

As of February 2005, the FWA is the only type of new assurance of compliance accepted and approved by OHRP for institutions engaged in nonexempt human subjects research conducted or supported by the DHHS. FWAs also are approved by OHRP for federalwide use, which means that other departments and agencies that have adopted the Common Rule may rely on the FWA for the research that they conduct or support. Institutions engaging in research conducted or supported by non-DHHS federal departments or agencies should consult with the sponsoring department or agency for guidance regarding whether the FWA is appropriate for the research in question.

Institutions holding an OHRP-approved MPA or CPA are required to submit an FWA to OHRP for approval by December 31, 2005, if the institution is required to have an OHRP-approved assurance of compliance. SPAs currently approved by OHRP will remain in effect for the duration of the project and through all noncompetitive award renewals.

MPA institutions were grandfathered in to the IRB/IEC registration system on December 4, 2000.

⁵See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

Key Concepts: IRB Registration and Assurances of Compliance

- Institutions receiving federal funds for research from agencies that are signatories to the Common Rule must provide an assurance of compliance to either OHRP or the funding agency as a condition of receipt of funds.
- Each legally separate institution must obtain its own FWA, and assurances approved under this process will cover all the institution's federally supported research involving human subjects.
- OHRP now offers one assurance option: the FWA.
- Obtaining an approved assurance from OHRP requires that the institution ensure that the IRB designated under the assurance is registered with OHRP. Registration of IRBs is required regardless of whether they review research sponsored or are regulated by a federal agency that follows the Common Rule.
- FDA does not require its sponsors to provide assurances of compliance.
- If research is conducted or supported by a non-DHHS agency that is also a signatory to the Common Rule, then the non-DHHS agency must have an assurance with the funding agency or with DHHS, whichever agency has been designated.
- An institution with an approved assurance must certify that each application or proposal for research covered by the assurance has been reviewed and approved by the IRB covered by the assurance.
- Assurances can be provided by non-U.S. institutions conducting federally funded research under similar, but not identical, terms as those applied to U.S. institutions.

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Chapter 6

Regulatory Compliance and Oversight

- A. Introduction
 - B. Food and Drug Administration Enforcement Mechanisms
 - C. Mechanisms for Enforcement
- Key Concepts**
Reference



A. Introduction

Although the current regulatory framework for research with human subjects generally is implemented at the local or institutional level, federal regulatory and funding agencies also have oversight. Federal enforcement measures help make all parties aware that human subjects protection must be taken seriously, and they ensure the public's continuing trust in this area. When investigators or institutions are unwilling or unable to provide appropriate protection to research subjects, enforcement action can prevent individuals and possibly their institutions from conducting human research. Enforcement should complement policy, education, and monitoring of compliance to ensure that research participants are protected; however, it should not be the primary focus of an oversight system (NBAC 2001).

As noted in previous chapters of this manual, in the United States the core aspect of the Federal Policy for the Protection of Human Subjects, known as the Common Rule, has been the regulatory policy followed by 16 federal departments and agencies for protecting human research subjects. Each codification of the Common Rule by a department or agency is equivalent to 45 CFR 46.101-46.124 (Subpart A), the Department of Health and Human Services (DHHS) codification.¹ The Common Rule applies to all research that involves human subjects “conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make this

policy applicable to such research” (§___101(a)). The Food and Drug Administration (FDA) also has its own regulatory authority over research involving food and color additives; investigational drugs, medical devices, and biological products for human use being developed for marketing; and electronic products that emit radiation (21 CFR 50, 56).² FDA applies its own set of regulations, which is generally but not entirely the same as the Common Rule. FDA can conduct site inspections of institutions or Institutional Review Boards (IRBs). Under its regulations, FDA can withhold approval of new studies, prohibit enrollment of new subjects, and terminate studies. FDA also can issue warning letters and can restrict or disqualify investigators, IRBs, or institutions from conducting or reviewing research with investigational products.

Some agencies have promulgated additional regulations concerning the protection of human subjects in research—in particular, those related to privacy. For example, the Department of Education complies with the Family Education Rights and Privacy Act of 1974 (20 USC § 1232g; 34 CFR Part 99), which is designed to protect student records from disclosure without consent from parents or students over 18 years of age. The Department of Justice provides additional regulatory protections for prisoners (28 CFR 512) that give prisoners control over their data, require at least one prisoner and a majority who are not prison personnel to be members of the IRB reviewing the research, and prohibit prison administrators from accessing research

¹ See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

² See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html and www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html.

data. Additional confidentiality protections are provided in the National Center for Educational Statistics Confidentiality Statute and the Public Health Service Act for the Centers for Disease Control and Prevention's assurance of confidentiality (see also Chapter 13 on privacy).

Such federal regulations give department and agency heads the authority to terminate or suspend funding for research projects that are not in compliance with the regulations (§____.123(a); 21 CFR 56, Subpart E). Common enforcement tools are the requirement of written responses

authority to terminate or suspend funding

or the enactment of specific changes to address the identified deficiencies; those who grant assurances also can restrict or suspend institutional

assurances (see Chapter 5 for a discussion of the assurance process). Manuals provided by specific agencies/offices may contain additional information on specific agency/office requirements.

Federal oversight of regulated research can occur for cause or not for cause. The latter approach typically involves assessing institutional, IRB, and investigator compliance to help ensure that standards are being followed consistently. As discussed in Chapter 5, the major mechanism for this type of assessment is the assurance of compliance issued by DHHS through the Office for Human Research Protections (OHRP) and through other federal departments that issue their own assurances (for example, the Department of Defense). Institutions receiving non-DHHS federal support that have assurances of compliance from OHRP are subject to enforcement from the funding agencies as well as OHRP. In the case of DHHS grantees and contractors, the enforcement authority is clear because OHRP is part of DHHS. However, when the assurance holder is the grantee of another department, OHRP decisions come from outside the regular reporting line of authority. Additionally, departments that use the OHRP assurance process may also have their own separate systems for enforcement.

At the local level, some institutions have established ongoing mechanisms for assessing investigator compliance with regulations. However, institutions vary considerably in their efforts and abilities to monitor investigator compliance from those that have no monitoring programs to those that conduct random audits.

This chapter focuses on the enforcement and oversight mechanisms available to FDA and OHRP through regulation, recognizing that other federal agencies and institutions might have additional mechanisms in place to ensure that sponsored research is conducted according to all relevant federal rules and regulations.

B. FDA Enforcement Mechanisms

FDA has several enforcement options available when the conduct of clinical research is found to be out of compliance with applicable FDA regulations or when fraudulent or otherwise unreliable clinical trial data are submitted to FDA in a marketing application. Under the agency's Bioresearch

inspections

Monitoring (BIMO) Program, FDA conducts inspections of sponsors, monitors, contract research organizations (CROs), clinical investigators, IRBs, and bioequivalence facilities (see Chapter 16 for more detail about FDA, in general). FDA conducts onsite procedural reviews of IRBs to determine whether an IRB is operating in accordance with its own written procedures as well as in compliance with current FDA regulations affecting IRBs. (These regulations include 21 CFR Part 50 [Informed Consent], Part 56 [Standards for IRBs], Part 312 [Investigational New Drugs], and Part 812 [Investigational Devices]).

When a marketing application is submitted to the agency, the BIMO program of the FDA center³ with jurisdiction over the product selects several clinical study sites and issues assignments to FDA's field offices to inspect the sites. The center also may issue assignments to inspect the sponsor, the IRB, the monitor, or a CRO related to the study. The purpose of these inspections is to (1) verify the integrity of the data submitted to the agency, 2) protect the rights and welfare of the study subjects, and 3) determine whether the clinical investigator or sponsor, or IRB or other facility, complied with FDA's regulations for the conduct of the study. FDA inspects about 250 to 300 IRBs each year as part of its routine surveillance program.⁴

FDA Inspections of Clinical Investigators

FDA carries out three distinct types of clinical investigator inspections: (1) study-oriented inspections, (2) investigator-oriented inspections, and (3) bioequivalence study inspections. Bioequivalence study inspections are conducted because one study may be the sole basis for a drug's

³ The FDA's five centers (the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine) and the Office of Regulatory Affairs jointly administer and coordinate inspection policy for the Bioresearch Monitoring Program.

⁴ The conduct of each of these inspections is described in the respective FDA Compliance Program Guidance Manuals, found on FDA's Web site at www.fda.gov/oc/gcp/compliance.html.

marketing approval. The bioequivalence study inspection differs from the other inspections in that it requires participation by an FDA chemist or an investigator knowledgeable about analytical evaluations. The other two types of inspections are discussed in more detail below.

Study-Oriented Inspections. FDA field offices conduct study-oriented inspections on the basis of assignments developed by headquarters staff. Assignments are based almost exclusively on studies that are important to product evaluation, such as new drug applications and product license applications pending before the agency.

The investigation consists of two basic parts. The first part involves determining the facts surrounding the conduct of the study, including:

- who did what
- the degree of delegation of authority
- where specific aspects of the study were performed
- how and where data were recorded
- how test article accountability was maintained
- how the monitor communicated with the clinical investigator
- how the monitor evaluated the study's progress

Second, the study data are audited. The FDA investigator compares the data submitted to the agency and/or the sponsor with all available records that might support the data. These records may come from the physician's office or a hospital, nursing home, laboratories, or other sources. FDA also may examine patient records that predate the study to determine whether the medical condition being studied was, in fact, properly diagnosed and whether a possibly interfering medication had been given before the study began. The FDA investigator also may review records covering a reasonable period after completion of the study to determine whether there was proper follow-up and whether all signs and symptoms reasonably attributable to the product's use had been reported.

Investigator-Oriented Inspections. An investigator-oriented inspection may be initiated when an investigator has conducted a pivotal study that merits indepth examination because of its singular importance in product approval or its effect on medical practice. An inspection also may be initiated because representatives of the sponsor have reported to FDA that they are having difficulty getting case reports from the investigator or that they have some other concern with the investigator's work. In addition, the agency may initiate an inspection if a subject in a study complains about protocol or subject rights violations. Investigator-oriented inspections also may be initiated because clinical investigators have participated in a large number of studies or have done work outside their specialty areas. Other

reasons include safety or effectiveness findings that are inconsistent with those of other investigators studying the same test article; the claiming of too many subjects with a specific disease given the locale of the investigation; or laboratory results that are outside the range of expected biological variation.

Once the agency has determined that an investigator-oriented inspection should be conducted, the procedures are essentially the same as those for the study-oriented inspection, except that the data audit goes into greater depth, covers more case reports, and may cover more than one study. If the investigator has repeatedly or deliberately violated FDA regulations or has submitted false information to the sponsor in a required report, FDA will initiate actions that may ultimately determine that the clinical investigator is not to receive investigational products in the future.

FDA Inspection Findings

If an FDA inspector identifies examples of noncompliance with the regulations, the examples are noted on FDA Form 483, Inspectional Observations. All observations must be traceable back to a regulation, either final or interim. FDA inspections may not cite violations of draft (proposed) regulations or of guidance documents. However, failure to comply with an element of a guidance document can be construed to reflect failure to comply with an underlying regulation. A copy of the completed Form 483 is provided to the inspection site at the end of the inspection. FDA permits annotation of the form if the inspected party can show the FDA investigator that an observation is incorrect or is in the process of being corrected. Thus, it is important for the inspected site to make every effort to negotiate such annotations before the FDA investigator concludes the inspection and leaves the premises.

failure to comply with an underlying regulation

At the conclusion of an inspection, regardless of whether a Form 483 is issued, the FDA inspector will write an Establishment Inspection Report (EIR). The EIR, along with copies of the Form 483 and any supporting documentation collected at the site, will be filed or used for further enforcement action. The party that has undergone an FDA inspection should submit a written Freedom of Information Act (FOIA) request for a copy of the EIR to the local FDA district office. The FDA inspector should be asked to provide the address before the inspection concludes. Typically, 30 days should be allowed to elapse before filing the request because it may take that long for the EIR review and approval process to be completed. If FDA is considering an enforcement action, it may not release the EIR.

All FDA inspections receive a final classification, which indicates one of the following:

- NAI (No Action Indicated)— No objectionable conditions or practices were found, and they do not justify further regulatory action.
- VAI (Voluntary Action Indicated)— Objectionable conditions or practices are found, but FDA is not prepared to take administrative or regulatory action; however, corrective actions are required and a follow-up inspection may occur.
- OAI (Official Action Indicated)— Regulatory and/or administrative actions will be recommended; a follow-up inspection is likely.

A notice of the inspection's classification should be received by the inspected site within about 45 days, and, if it is not, a letter requesting that information should be sent to the district office. If the inspection yielded no Form 483 items, FDA might send a letter of appreciation for cooperating during the inspection, indicating that the inspected party is in compliance with the regulations. If a small number of minor observations were identified, a follow-up letter may be sent offering some suggestions on improving the observations that were recorded. However, if objectionable observations were noted during the inspection (as documented on the Form 483), and FDA decided to take further regulatory or administrative action, FDA may consider a number of follow-up actions. These are described below.

Untitled Letter. An untitled letter is a letter from FDA that has no other title, in contrast to "titled" letters, such as a Warning Letter (WL) or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter (see next column). An untitled letter is sent to document minor deviations from the regulations, typically seen in inspections that were classified NAI or VAI. Any inspection classified OAI would not receive an untitled letter, but rather would be subject to one or more enforcement actions (see below).

FDA's expectation is that the recipient will respond to an untitled letter in a reasonable period of time (or within the time requested by FDA) with a list of corrective actions that the inspected party intends to implement that should prevent the observed violations from occurring again. FDA may accept a written response and pursue no further action if it determines the response is adequate. Also, FDA could decide to schedule a follow-up inspection after a period of time to ensure the corrective actions were put into place. Untitled letters typically would not be used for violations that merit a follow-up inspection. There are other options FDA can use in that circumstance.

Warning Letter (WL). For inspections where numerous and/or serious violations are found, FDA may issue a WL. This so-called "titled letter" is a more severe enforcement action than an untitled letter and requires a greater level of FDA scrutiny and approval before it is issued. In addition, it is issued as an official action, thus requiring that the subject inspection be classified OAI. It is considered an advisory letter communicating the requirements for correction of serious deviations. It is publicly available and is published on FDA's Web site soon after issuance.⁵

As with the untitled letters, FDA will expect a response within a certain period of time—in this case, a mandatory 15 days—and will review the proposed corrective actions carefully. If one or more corrective actions are considered inadequate, additional correspondence will follow and a follow-up inspection may be conducted to verify the corrective actions. If the WL does not yield the expected corrective actions, FDA will then consider pursuing more severe enforcement actions.

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter. This titled letter is intended to inform the recipient clinical investigator that FDA is initiating an administrative proceeding to determine whether the investigator should be disqualified from receiving investigational products. Generally, FDA issues a NIDPOE letter when it believes it has evidence that the investigator repeatedly or deliberately violated FDA's regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to FDA or the sponsor. The NIDPOE letter and its attendant violations may or may not have been preceded by the issuance of a WL. Detailed regulations about the NIDPOE letter are found in FDA investigational new drug regulations at 21 CFR 312.70.⁶

The typical chain of events is that FDA issues the NIDPOE letter and the investigator provides a response (the opportunity to explain). A NIDPOE letter also may include the terms of a consent agreement (see below), which the investigator may opt to select rather than respond to the violations cited in the letter. The investigator may submit a written response that explains the violations or may request an informal conference to discuss the contents of the NIDPOE letter. An attorney is welcome to accompany the investigator to the informal conference. If FDA accepts the response, it may decide to terminate the disqualification process. If the response is determined to be inadequate to address the violations or if the investigator chooses not to reply to the NIDPOE letter, a Notice of Opportunity for Hearing (NOOH) is issued.

⁵ To view representative WLs, see www.fda.gov/foi/warning.htm, and select the appropriate letters under the appropriate category.

⁶ NIDPOE letters are posted on FDA's Web site at www.fda.gov/foi/nidpoe/default.html.

The NOOH provides an individual with the opportunity for a hearing on the proposed enforcement action (i.e., the disqualification) before a presiding officer designated by the FDA Commissioner. The investigator has an opportunity to waive a hearing, in which case a final decision will be made on the proposed enforcement action, or to request a hearing. If he/she requests a hearing, the request must provide a basis for disputing the facts (that is, of the inspection findings), and if the investigator cannot provide an adequate basis for disputing those facts, a hearing may be denied. A formal hearing is offered and conducted according to FDA regulations found at 21 CFR 16.

Restriction. FDA may allow the investigator to enter into restricted agreements when it believes that enforcement actions lesser than disqualification would be adequate to protect the public health. The investigator would still be eligible to receive investigational products, provided he/she conducted regulated studies in accordance with the restrictions specified in the agreement with FDA and all applicable regulatory requirements. Examples of restrictions include studies requiring prior FDA approval, work proceeding under a supervising proctor, and limitations being placed on the number of studies the investigator may conduct and the number of subjects that may be enrolled in each study.⁷ Restrictions, which are specifically indicated for each investigator on the corrective actions list, may be lifted at FDA's discretion.

Disqualification (total restriction). Investigators who are disqualified are ineligible to receive investigational products, as determined through the regulatory hearing process described above, until such time that they are reinstated by FDA (if ever). Thus, they may not conduct any FDA-regulated research.⁸ Again, FDA will disqualify an investigator who has repeatedly or deliberately failed to comply with FDA regulations or who has submitted false information to the sponsor. Disqualification does not affect the ability of the investigator to practice medicine, however, because medical licensing is regulated by the state, not FDA. Nor does it prevent the investigator from conducting research that is not FDA regulated. A typical case may take two to four years before all the proceedings are completed. Disqualification does not prevent FDA from pursuing criminal action against an investigator who has committed fraud (see below).

Consent Agreement. The consent agreement is a voluntary agreement between the appropriate FDA review

center (drugs, biologics, or medical devices) and the investigator. It is offered as an option at the beginning of the formal disqualification process. By consenting to disqualification, the investigator may incur a lesser degree of restrictions on his/her ability to conduct FDA-regulated research, and the process occurs more rapidly than formal disqualification proceedings, which, as indicated above, can take several years.

Enforcement Actions Against Sponsors

Except for the WL, the enforcement actions described above typically are applied against an investigator for violations found during an FDA inspection. A WL could be issued to a sponsor that did not adequately monitor a clinical trial or properly manage investigational product accountability and some other combination of violations of FDA regulation-defined sponsor responsibilities. The FDA *Compliance Program Guidance Manual* would describe those activities from the standpoint of an FDA inspection.⁹ In addition to the WL, the following enforcement actions may be applied specifically against the sponsor of the clinical research. In the case of a sponsor-investigator, all actions are possible.

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A *clinical hold* is an order issued by FDA to the sponsor to either delay a proposed clinical investigation (i.e., when an Investigational New Drug application has been submitted, but FDA has strong reservations about the proposed study) or to suspend an ongoing investigation (i.e., when an FDA inspection has raised concerns about the study or about the investigator conducting the study). In the latter case, no new subjects may be recruited to the study, and subjects already in the study should be taken off the investigational therapy unless specifically permitted by FDA in the interest of patient safety.

An August 27, 2002, FDA draft guidance document, entitled *The Use of Clinical Holds Following Clinical Investigator Misconduct*, listed the many reasons that would cause FDA to consider a clinical hold during an ongoing study.¹⁰ Typically, these involve misconduct on the part of the investigator, where FDA believes that human subjects are being or would be exposed to an unreasonable and significant risk of illness or injury. A clinical hold may be imposed either before or after other enforcement actions have been taken.

⁷ FDA provides a list of restricted investigators at www.fda.gov/ora/compliance_ref/bimo/restlist.htm.

⁸ A list of disqualified investigators is provided at www.fda.gov/ora/compliance_ref/bimo/disqlist.htm.

⁹ See www.fda.gov/ora/cpgm/default.htm.

¹⁰ See www.fda.gov/OHRMS/DOCKETS/98fr/02d-0320-gdl0002.pdf.

When FDA determines there are problems with a particular sponsor, in particular a pattern of wrongful acts, such as untrue statements, the submission of a fraudulent application, a pattern of errors, or a system-wide failure to ensure the integrity of submissions, FDA may decide to impose its Application Integrity Policy (AIP) on that sponsor. The AIP describes FDA's approach regarding the review of marketing applications that may be affected by these acts in cases in which FDA believes there are significant questions regarding the reliability of data submitted in those applications. The AIP allows FDA to exclude data or delay the approval of an application (e.g., a New Drug Approval or NDA) or to withdraw an approved application. The policy would apply to all applications from the sponsor whose integrity is in question.

the use of clinical holds following clinical investigator misconduct

The enforcement actions noted above are considered administrative actions. The following discussion reviews certain available civil actions and criminal actions that FDA may bring to bear on either a sponsor or an investigator who repeatedly or deliberately disregards FDA regulations.

FDA Civil and Criminal Actions

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives FDA the authority to impose two particular civil actions: injunction and seizure. These could be used in the context of clinical trials but generally are not. Section 302 of the FD&C Act permits the courts to issue a restraining order (injunction) to prevent a person or company from carrying out any of a list of prohibited acts that are listed in section 301 of the FD&C Act. These acts may include refusing to permit an FDA inspection or making false or misleading statements or reports. An injunction may be temporary or permanent (consent decree for permanent injunction). A person who is the subject of an injunction has been enjoined. Section 304 of the FD&C Act permits FDA to seize any adulterated or misbranded products. For example, if a clinical trial was being conducted with an investigational product that was judged to be hazardous, FDA could use this authority to seize and condemn the investigational product from the sponsor.

Individuals or companies can be criminally prosecuted under Title 18 of the U.S. Criminal Code for fraud (wire, radio, and television), making false statements to the government, conspiracy, obstruction of justice, and mail fraud, among other things. In order to file civil or criminal charges, FDA must make a recommendation to the Department of Justice, which will file the charge in District Court and may try the case with FDA lawyers and United States attorney(s), on behalf of the agency. Criminal prosecutions of investigators are infrequent, but they do occur, and if successful they can result in felony convictions.

Debarment. Section 306 of the FD&C Act provides FDA with the authority to impose a punishment called debarment, which is different from disqualification. Debarment applies to an individual (or firm) convicted of a felony crime relating to the drug development or approval process. A person who is debarred cannot work in any capacity for a drug firm, and FDA will not accept or review applications involving debarred persons or companies. Debarment may be either permissive (five years) or mandatory (one to 10 years for a firm and permanently for an individual).

C. Mechanisms for Enforcement

OHRP has a different approach than FDA to enforcing the regulations, using its assurance process as the lever for achieving compliance. At the institutional level, OHRP sanctions are imposed when systematic deficiencies and concerns regarding systemic protections for research subjects are found. The deficiencies could be in such areas as IRB membership; education of IRB members and investigators; institutional commitment; initial and continuing review of protocols by IRBs; review of protocols involving vulnerable persons; or procedures for obtaining voluntary informed consent. In addition, other federal agencies or departments that offer an assurance process are likely to have their own procedures for enforcement. If the reader's institution does not have an OHRP-issued assurance, it is important to understand the policies and procedures of the agency with which the assurance of compliance has been negotiated.

OHRP's Assurance System

As discussed in Chapter 5, the assurance process is the primary mechanism by which OHRP, on behalf of the Secretary of DHHS, sets forth the means by which an institution will comply with the regulations. Many federal agencies that are signatories to the Common Rule rely solely on the OHRP assurance process for guaranteeing the compliance of their grantees, although some agencies also negotiate their own assurances.

The lever of this system of enforcement is that assurances are given by institutions as a condition of receipt of DHHS or other federal support for research involving human subjects. An assurance approved by OHRP commits the institution and its personnel to full compliance with the human subjects regulations. Assurances are required by §____.103 of the Common Rule (not adopted by FDA) and must be on file at OHRP. The content of the assurance includes a statement of principles governing the

assurances are given by institutions

institution in the discharge of its responsibilities for protecting human subjects, designation of one or more IRBs, a list of IRB members, written procedures for the operation of the IRB, and written procedures for reporting adverse events or incidents of noncompliance.

In general, institutions assure the government that all research conducted at the institution—whether federally funded or not—will be conducted in compliance with the regulations, although the government only has jurisdiction over that which is federally funded or regulated. While recognizing both individual and institutional responsibility for compliance with the regulations, OHRP generally negotiates assurances only with institutions that are ultimately responsible for ensuring that the regulatory requirements are met. Investigators and IRBs, however, also retain responsibility for complying with the regulations. OHRP holds accountable and depends on institutional officials, committees, research investigators, and other agents of the institution to assure conformance with the institution's assurance and thus with the regulations.

Other mechanisms and authorities also are in place to monitor and oversee the research enterprise. For example, in 1992 the Office of Research Integrity was reorganized within DHHS and was charged with overseeing investigator misconduct and prevention activities in DHHS-funded research, except for those investigators who fall under FDA jurisdiction. Investigative and oversight units of the executive branch and Congress have the authority to oversee various aspects of the research enterprise and report on its status. Actions also can be taken at the recommendation of an agency's Office of Inspector General, and Congress reserves the right to intervene through the budget process or its investigatory powers. However, other than FDA's system of oversight, the most common mechanism used to ensure compliance with the Common Rule is through actions taken by OHRP.

Considerations for Ensuring Compliance

The Common Rule requires that institutions follow written procedures for ensuring that serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB will be reported to the IRB, appropriate institutional officials, and the head of the department or agency supporting the research (§____.103(b)(5)). Each institution is responsible for establishing the mechanism through which instances of noncompliance will be reported to the department or agency.

To ensure compliance with the regulations, many institutions adopt internal audit or self-assessment procedures and practices designed to assure proper protocol and

consent document preparation, protocol submission, review and approval by the IRB, and timely monitoring of protocol implementation.

Noncompliance by Investigators, IRBs, and Institutions

Investigators. Research investigators are the most frequent source of noncompliance with human subjects regulations. According to OHRP, the most common lapses in investigator compliance include unreported changes in protocols, misuse or nonuse of the informed consent document, and failure to submit protocols to the IRB in a timely fashion. Problems such as these are often caused by communication difficulties. With the cooperation of the investigator, many of these cases can be resolved by the IRB without jeopardizing the welfare of research subjects.

Occasionally, an investigator will either avoid or ignore an IRB and its recommendations. Such cases present a more serious challenge to the IRB and the institution. Regardless of investigator intent, unapproved research involving human subjects places those subjects at an unacceptable risk. When unapproved research is discovered, the IRB and the institution should act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subjects protection requirements, and address the question of the investigator's fitness to conduct human subjects research. Beyond the obvious need to protect the rights and welfare of research subjects, the credibility of the IRB is clearly at stake. In addition, any serious or continuing noncompliance with human subjects regulations or the determinations of the IRB must be promptly reported to OHRP (or the department or agency head).

IRBs. IRB noncompliance occurs whenever the IRB deviates from the duties imposed on it by the federal regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective subjects to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable subjects; and failing to conduct continuing review of research at intervals appropriate to the degree of risk. IRBs also breach their regulatory responsibilities by failing to maintain adequate records of IRB business and by failing to hold their meetings with a majority of members present, including a nonscientific member. A demonstrated inability to carry out IRB responsibilities in accordance with the regulations can be cause for

**IRB
noncompliance**

the suspension or withdrawal of approval of an institution's assurance (see below).

Institutions. Although institutions are accountable for the actions of individual investigators and the IRB, institutional noncompliance is more broadly described as a systemic failure of the institution to implement practices and procedures contained in the institution's assurance. Prime examples are the failure of the institution to ensure that the IRB is appropriately constituted and functions in accordance with the regulations, that the IRB receives appropriate institutional support and staffing, and that investigators meet their obligations to the IRB. Systemic failure to abide by the terms and conditions of an institution's assurance will result in withdrawal of approval of the assurance (see below).

External Audits and Site Visits

Regulatory compliance can be promoted via routine site visits and audits conducted by federal officials. FDA monitors IRB compliance through a program of regular onsite inspections of IRB minutes and records. In contrast, OHRP conducts occasional site visits to institutions to assess the adequacy of their procedures for protecting human research subjects. These visits can be conducted for cause or without cause. In addition, sponsors of research, such as the National Cancer Institute, and cooperative group research organizations regularly audit their research performance sites. These audits normally include an examination of IRB minutes and records for conformance with applicable regulations. The results of these audits generally are shared with OHRP and FDA. Onsite assessments of this nature are generally designed to instruct and educate rather than to investigate and sanction.

for cause or without cause visits

Investigations of Alleged Noncompliance

As warranted, both FDA and OHRP conduct inquiries or investigations into alleged noncompliance with federal regulations. The need for site visits in connection with inquiries and investigations depends on the seriousness and urgency of the circumstances and whether onsite involvement is the most effective means of resolving the questions of noncompliance that have been raised. Federal inquiries and investigations into alleged noncompliance with the regulations are not undertaken lightly. Experience has shown that these efforts are usually initiated in response to credible reports of inappropriate involvement of human subjects in research. Such reports can come from any source: investigators, subjects, institutional personnel, IRB members, the general public, or the media. The Common Rule does not specify administrative actions for noncompliance with the human subjects regulations, except to state

that material failure to comply with the regulations can result in termination or suspension of support for department or agency projects and that DHHS or the relevant federal agency will take terminations or suspensions of funding resulting from noncompliance into consideration when making future funding decisions (§____.123).

OHRP compliance oversight procedures are called compliance oversight evaluations. Before responding to alleged noncompliance, OHRP must first determine that it has jurisdiction on the basis of DHHS support and/or an applicable assurance of compliance.

When OHRP initiates a compliance oversight evaluation, appropriate institutional officials are advised, and they are informed regarding the likely administrative course of events. Activities expected of the institution are carefully explained initially and at appropriate times during the course of the evaluation. Where the allegations of possible noncompliance involve a specific research investigator, OHRP notifies the investigator involved.

Except in rare circumstances that dictate the need to act immediately, OHRP takes no action against any institution without first providing the institution an opportunity to offer information that might refute or mitigate adverse determinations. In all cases, appropriate institutional officials are given an opportunity to comment in writing before OHRP issues its findings. The institutional official responsible for the assurance is asked to investigate the matter and report to OHRP by a specified date.

Documents related to compliance oversight evaluations may be subject to the provisions of FOIA. In most cases, such documents are exempt from the disclosure provisions of FOIA while the evaluation is in progress, and OHRP treats them with confidentiality. However, OHRP routinely advises appropriate DHHS officials concerning the status of its evaluations and may be required to inform members of Congress. Most documents related to compliance oversight evaluations become publicly available under FOIA when OHRP issues its findings. However, the institution can request confidentiality under an exemption in the privacy regulations if the information in the compliance letter relates to proprietary information. OHRP may request that the institution submit additional information in writing, conduct telephone interviews with institutional officials, committee members, or investigators, or conduct onsite evaluations.

Under DHHS regulations at 45 CFR, Part 5b, records that can be retrieved by an individual's name or other personal identifier are subject to the provisions of the Federal Privacy Act. Information regarding OHRP's compliance oversight activities is maintained only in a system of records identifying the institution under evaluation. OHRP

maintains no system of records related to compliance oversight activities through which records can be retrieved by individuals' names or other personal identifiers.

Possible Outcomes of an OHRP Investigation

Corrective actions based on compliance oversight evaluations are intended to remedy identified noncompliance and to prevent reoccurrence. OHRP tailors the corrective actions to foster the best interest of human subjects and to the extent possible, the institution, the research institutions, the research community, and DHHS or the relevant funding agency. Most corrective actions are resolved at the OHRP level; however, OHRP reserves the right to recommend that actions be taken by other federal officials. OHRP's compliance oversight evaluations could result in one or more of the following outcomes:

- OHRP may determine that protections under an institution's assurance are in compliance with the regulations.
 - OHRP may determine that protections under an institution's assurance are in compliance with the regulations but that recommended improvements to those protections have been identified.
 - OHRP may determine that protections under an institution's assurance are not in compliance with the regulations and require that an institution develop and implement corrective actions.
 - OHRP may restrict its approval of an institution's assurance. Affected research projects cannot be supported by DHHS or the relevant agency until the terms of the restriction have been satisfied. Examples of such restrictions include, but are not limited to:
 - Suspending the assurance's applicability relative to some or all research projects until specified protections have been implemented
 - Requiring prior OHRP review of some or all research projects to be conducted under the assurance
 - Requiring that some or all investigators conducting research under the assurance receive appropriate human subject education
 - requiring special reporting to OHRP
- OHRP may withdraw its approval of an institution's assurance. Affected research projects cannot be supported by any DHHS component or the relevant agency until an appropriate assurance is approved by OHRP.
 - OHRP may recommend to appropriate DHHS or other agency officials:
 - That an institution or an investigator be temporarily suspended or permanently removed from participating in specific projects; and/or
 - That peer review groups be notified of an institution's or an investigator's past noncompliance prior to review of new projects.
 - OHRP may recommend to DHHS or other agency officials that institutions or investigators be declared ineligible to participate in federally supported research (debarment). If OHRP makes this recommendation, the debarment process is initiated in accordance with the procedures specified at 45 CFR 76. Any debarment is government wide and does not apply only to DHHS funding.

OHRP issues, in writing, a determination letter for each evaluation, addressed to a signatory official and other appropriate institutional officials. The determination letter summarizes the findings of noncompliance, if any, and describes the corrective actions proposed and/or implemented by the institution to address the findings. OHRP determination letters are posted on the OHRP Web site (www.hhs.gov/ohrp/) once the document has been requested under FOIA or 10 working days after the document is issued to the institution, whichever occurs first.

Key Concepts: Regulatory Compliance and Oversight

- Federal regulatory agencies employ two basic approaches for ensuring compliance with the Common Rule. FDA uses a system of inspections and audits. In contrast, other federal agencies rely prospectively on assurances of compliance that are negotiated with institutions by OHRP or that are developed through their own assurance process.
- FDA regulations provide specific administrative action and sanctions for noncompliance (21 CFR 56.120-24), which the Common Rule does not.
- FDA can conduct site inspections of institutions or IRBs. Under its regulations, FDA can withhold approval of new studies, prohibit enrollment of new subjects, and terminate studies. FDA also can issue WLs and can restrict or disqualify investigators, IRBs, or institutions from conducting or reviewing research with investigational products.
- The FD&C Act gives FDA the authority to impose two particular civil actions: injunction and seizure.
- Federal regulations give department and agency heads the authority to terminate or suspend funding for research projects that are not in compliance with the regulations.
- Federal oversight of regulated research can occur for cause or not for cause.
- Federal agencies and institutions with assurances of compliance from OHRP are subject to enforcement from that office as well as to any additional measures implemented by the sponsoring agency.
- The Common Rule requires that institutions follow written procedures for ensuring that serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB will be reported to the IRB, appropriate institutional officials, and the head of the department or agency supporting the research. Each institution is responsible for establishing the mechanism through which instances of noncompliance will be reported to the department or agency.
- At the institutional level, OHRP sanctions are imposed when systematic deficiencies and concerns regarding systemic protections for research subjects are found. The deficiencies could be in such areas as IRB membership, education of IRB members and investigators, institutional commitment; initial and continuing review of protocols by IRBs, review of protocols involving vulnerable persons, or procedures for obtaining voluntary informed consent.

Reference

National Bioethics Advisory Commission (NBAC). 2001. *Ethical and Policy Issues in Research Involving Human Participants, Volume 1*. Rockville, MD: U.S. Government Printing Office. Available at www.georgetown.edu/research/nrcbl/nbac/human/overvol1.pdf.

Chapter 7

Institutional Review Board Membership

- A. Introduction
 - B. Institutional Review Board Membership Requirements
 - C. Types of Members
 - D. Recruitment and Retention of Institutional Review Board Members and Chairpersons
 - E. Institutional Review Board Training, Continuing Education, and Professional Development
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A. Introduction

Each institution engaged in research involving human subjects that is subject to the Federal Policy for the Protection of Human Subjects (the Common Rule) or Food and Drug Administration (FDA) regulations must designate one or more Institutional Review Boards (IRBs) to review and approve the research. The appropriate numbers of IRBs designated by an institution depend on the structure of the institution and the types of research (e.g., biomedical research, social and behavioral science, gene transfer) and volume of human subjects research performed at that institution. Furthermore, an institution can designate another institution's IRB to review some or all of its research with the concurrence of the designated IRB and upon approval of the appropriate department or agency. If the research is supported by the Department of Health and Human Services (DHHS), such designations must have the prior approval of the Office for Human Research Protections (OHRP).

Typically, the IRB is the administrative body established to

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protect the rights and welfare of human research subjects in research activities conducted under the auspices of the institution with which it is affiliated. However, IRBs also can be freestanding and can serve central and coordinating

functions across multiple institutions.

The IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations (§___.109(a); 21 CFR 56.109(a)) and local institutional policy (see Chapter 6). Thus, the IRB plays a central review role in a human subjects research protection program, with the effectiveness of the review process depending on the experience and commitment of board members and staff.

IRB members should be able to make complex judgments that require both the ability to assess the ethical appropriateness of the research design and methodology and an awareness of the important elements that could minimize risk to subjects and affect the ability of potential subjects to refuse or consent to enroll. The IRB should include members who are especially well grounded in ethics and community values, given its primary function of assessing the ethical soundness of a research protocol. In addition, board membership must be diverse, representing scientific and nonscientific and institutional and noninstitutional interests.

This chapter addresses IRB membership, including the composition of the board, the need for diversity, the requirements regarding members with conflicting interests, the recruitment and retention of members, and the importance of education.

B. IRB Membership Requirements

Number and Background

IRBs must have at least five members, with varying backgrounds, to promote complete and adequate review of research activities commonly conducted by the institution (§____.107(a); 21 CFR 56.107(a)). Some IRBs are much larger, depending on the volume of research to be reviewed, and some institutions have established more than one IRB. An IRB can have as many members as needed to perform its duties effectively. Care should be taken, however, to ensure that it does not become so large that its management becomes cumbersome.

According to the Common Rule and FDA regulations, an IRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. It must also include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution (§____.107(c) and (d); 21 CFR 56.107(c),(d)).

Need for Diversity

Each IRB must be sufficiently qualified through the experience and expertise of its members and the diversity of its members—including considerations of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes—to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects (§____.107(a); 21 CFR 56.107(a)).

The IRB must make every effort to ensure that it does not consist entirely of men or entirely of women. Selections must not, however, be made solely on the basis of gender (§____.107(b); 21 CFR 56.107(b)).

Expertise

In addition to possessing the professional competence necessary to review specific research activities, an IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (§____.107(a); 21 CFR 56.107(a)). It must therefore include persons knowledgeable in these areas. For FDA-regulated research, in general it is beneficial to have one or more members who are licensed physicians with appropriate training and credentials. No IRB, however, may consist entirely of members of one profession (§____.107(b); 21 CFR 56.107(b)).

It would be impractical to require that every IRB member possess all the requisite expertise; rather, as a group, the full complement of knowledge should be provided within the IRB, and individuals should maintain a basic appreciation for all issues. IRB professional staff should have sufficient knowledge to facilitate the effective operation of the board and to support members, investigators, and organizations in their respective roles.

the full complement of knowledge should be provided within the IRB

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB (§____.107(f); 21 CFR 56.107(f)). These individuals serve as consultants and may not vote, although in practice their participation often influences the voting of the regularly seated members.

Terms of Appointments

The Common Rule and FDA regulations do not place any limits on the length of time an IRB member may serve on an IRB. The term of appointment to an IRB varies by institution; some institutions have adopted a three-year term for their IRB members. At the same time, it is not uncommon to encounter IRBs with indefinite terms of appointment and IRB members who have served for decades. Typically, an institutional official appoints members in consultation with the IRB chairperson and administrator. A member can resign before the conclusion of his/her term. In addition, members can be removed by appropriate designated institutional officials.

Required Documentation

For any IRB designated under a DHHS assurance of compliance approved by OHRP, a list of current IRB members must be submitted to OHRP and also retained by the institution with the IRB's records (45 CFR 46.103(b)(3) and 46.115(a)(5)).

changes in IRB membership

The list must identify members by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution (e.g., full-time employee, stockholder, unpaid consultant, or board member). Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of a DHHS-approved assurance (§____.103(a)) (see also Chapter 5 on assurances and IRB registration). In

the latter case, changes in membership are to be reported to OHRP (§____.103(b)(3) and §____.115(a)(5)). For research not covered by an assurance, the FDA regulations (21 CFR 56.115(a)(5)) require that a list of IRB members be maintained, containing much the same information as required in the DHHS regulations and the Common Rule.

Members with Conflicting Interests

No IRB member may participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (§____.107(e); 21 CFR 56/107(e); (see also Chapter 22 on conflicts of interest).

Responsibilities for Review

In addition to the use of the board as a whole, many IRBs employ what has come to be known as the “reviewer” system. Under this system, one or more reviewers are designated to present their findings based on a review of the application materials, providing an assessment of the soundness and safety of the protocol and recommending specific actions to the IRB. In some cases the primary reviewers may also lead the discussion of the study. The reviewers may be required to review additional material requested by the IRB for the purpose of the study. Under this system, each regular member of an IRB may be expected to act as a reviewer for assigned studies at convened meetings. Both primary and secondary reviewers may be assigned. The secondary reviewer, if assigned, adds to the discussion as necessary. However, not all IRBs use this system of review, with some relying on a system of subcommittees for the review of specific types of protocols that report back to the entire board.

C. Types of Members

Scientific Members

The Common Rule and FDA regulations require that IRBs possess “the professional competence necessary to review specific research activities” and include at least one member whose primary interests are in scientific areas (i.e., scientific member) (§____.107(a); 21 CFR 56.107(a)). IRB members who are physicians, nurses, or individuals with bachelor’s, master’s, or doctoral degrees in the basic sciences or social sciences generally are considered scientific members.

Most IRBs include physicians and/or doctoral-level scientists, which satisfies the requirements for at least one scientist member. An investigator can be a member of the

IRB. However, there is a stipulation that must be adhered to without exception: The investigator-as-member cannot participate in the review and approval process for any project in which he/she has a conflicting interest (§____.107(e); 21 CFR 56.107(e)). When the investigator-member has a conflicting interest in a research protocol undergoing initial or continuing review, he/she may only provide information requested by the IRB. Some IRBs ask that the member leave during the discussion and voting phases of the review and approval process; IRB minutes should reflect whether these requirements have been met. Although the issue of conflicting interest occurs most frequently with scientific members, members who are nonscientific or nonaffiliated also could have a conflicting interest (see Chapter 22 for an extensive discussion of conflicts of interest).

When the IRB reviews DHHS-conducted or DHHS-supported biomedical research or clinical investigations involving FDA-regulated products, the convened meeting must include at least one physician member having the appropriate and relevant licensure and credentials. Depending on the scope of research routinely reviewed, the IRB may need to include several physicians with different specialty and subspecialty training. If the proposed research is in the behavioral or social sciences, the IRB should include appropriate behavioral and social scientists (see also Chapter 17). To fulfill these needs, IRBs can supplement their membership with consultants.

When an IRB encounters studies that involve science that is beyond the expertise of the members, the IRB may use a consultant to assist in the review, as provided by §____.107(f) and 21 CFR 56.107(f).

Unaffiliated Members

Current federal regulations require that each “IRB have at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution” (§____.107(d); 21 CFR 56.107(d)). Although the regulations do not require that unaffiliated members should be present for an IRB to review a research protocol, institutions are free to make this stronger requirement.

unaffiliated members of the IRB can have primary concerns that are either scientific or nonscientific

The unaffiliated members of the IRB can have primary concerns that are either scientific or nonscientific. All efforts should be made to ensure that the unaffiliated members do not feel intimidated by the professionals on the IRB and that their services and viewpoints are fully utilized and recognized by the IRB.

Ideally, an IRB should include a member drawn from the local community at large from which subjects are recruited to participate in the research. The person selected should be knowledgeable about the local community and be willing to discuss issues and research from that perspective.

Given the requirement that every IRB must have at least five members, some IRBs have adopted a practice of maintaining a ratio of having one unaffiliated member serve on the board for every five members. (Under this scenario, an IRB with 10 members would have two unaffiliated members.)

In recent years, recommendations have been made to increase the overall percentage of unaffiliated members of IRBs because of growing concern about the possibility that IRBs are becoming more aligned with institutional goals and missions than with protecting research subjects. In particular, the involvement of institutional staff on IRBs has been questioned when citing the need for more unaffiliated members. In its compliance determinations, OHRP has noted that there might be a fundamental conflict of interest when institutional grants and contracts officials—whose professional role is to bring research funds into an institution—serve on an IRB.

The primary strategy for limiting the influence of inappropriate institutional interests on IRBs is to impose requirements on IRB membership. Various groups that have studied this issue have recommended that a specific percentage of IRB membership be comprised of unaffiliated individuals. For example, the National Bioethics Advisory Commission (NBAC) recommended:

Institutional Review Boards should include members who represent the perspectives of participants, members who are unaffiliated with the institution, and members whose primary concerns are in nonscientific areas. An individual can fulfill one, two, or all three of these categories. For the purposes of both overall membership and quorum determinations 1) these persons should collectively represent at least 25 percent of the Institutional Review Board membership and 2) members from all of these categories should be represented each time an Institutional Review Board meets (2001, 64).

The Institute of Medicine (IOM) committee that authored *Responsible Research: A Systems Approach to Protecting Research Participants* (2003) recommended that the goal of research organizations should be to assemble a board with at least 25 percent of its membership unaffiliated with the institution, not trained as scientists, and able to represent the local community and/or the participant perspective.

However, finding more than one appropriate unaffiliated member who is willing to serve on an IRB can be difficult.

Paying unaffiliated members for their efforts, as originally proposed in the *Belmont Report* by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission 1979) might improve the yield, but excessive compensation could call members' independence into question. Institutions must balance all considerations when trying to boost the number and activity of unaffiliated board members.

Special Appointments for Research Involving Vulnerable Populations

If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or physically or mentally disabled persons, consideration must be given to the inclusion on the IRB of one or more individuals who are knowledgeable about and experienced in working with these subjects (§____.107(a); 21 CFR 56.107(a)). For example, if an IRB regularly reviews research involving children, consideration must be given to including individuals with the relevant expertise—for example, a pediatrician, a pediatric nurse, or a pediatric social worker.

relevant expertise

Department of Education regulations require that when an IRB reviews research for one of its programs that purposefully requires the inclusion of disabled children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these subjects (34 CFR 350.3(d)2); 34 CFR 356.3(c)(2)).

IRB Chairperson

One of the most important actions to be taken in establishing an IRB is selecting the chairperson, which typically is done by an institutional official. The IRB chairperson should be a highly respected individual from within or outside the institution who is fully capable of managing the IRB and the matters brought before it with fairness, impartiality, and independence from external pressures. The task of making the IRB a respected part of the institutional community will fall largely on the shoulders of this individual. The IRB must be, and must be perceived to be, fair and impartial and immune from pressure by the institution's administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources. An important role for the IRB chairperson frequently is the recruitment and evaluation of new IRB members, who also must be able to maintain a good working relationship with the IRB administrator and staff (see Chapter 9).

fair and impartial and immune from pressure

In addition to chairing meetings of the IRB, the chairperson can perform or delegate to an appropriate IRB member expedited review when appropriate (see Chapter 10). The chairperson should be empowered to suspend the conduct of a study deemed to place subjects at unacceptable risk, pending IRB review. The chairperson also should be empowered, pending IRB review, to suspend the conduct of a study if he/she determines that an investigator is not following the IRB's requirements.

The institution may appoint a cochairperson or vice chairperson to assist or act on behalf of the chairperson in particular IRB matters and at IRB meetings, either as a general procedure or on a case-by-case basis. The chairperson also may delegate any of his/her responsibilities as appropriate to other qualified individuals (e.g., requesting that the IRB administrator make determinations of expedited review for minimal risk research protocols). Such delegation must be documented in writing and maintained by the IRB administrator.

Alternates

The Common Rule does not address the designation of alternate IRB members. However, IRBs can have alternate members if each alternate is linked to a specific IRB member. That is, the subject matter expertise of the regular member and the alternate should be similar. However, the "slot" only gets a single vote, even if both members attend a meeting. IRBs also can submit a roster listing a handful of alternate members, with no special detail or linking.

When approving assurances that are designating IRBs that include alternate IRB members, it should be assumed that, in general, with respect to the capacity in which the primary IRB member was intended to serve, each alternate IRB member has the experience, expertise, background, professional competence, and knowledge equivalent to that of the primary IRB member that the alternate would replace. As such, whenever an alternate member substitutes for a primary member of the IRB, the combined requirements of §___107(a) and 108(b) and 21 CFR 56.107(a) and 108(b) should remain satisfied.

The minutes of an IRB meeting should document the attendance of all primary and alternate IRB members who attended any part of it. When both a primary IRB member and his/her alternate attend the same IRB meeting, OHRP assumes that the primary member is acting as the official voting member of the IRB for the review of research protocols, unless the minutes clearly indicate otherwise.

A designated alternate IRB member certainly may substitute for the primary IRB member at any time during a

meeting. This most commonly occurs when the primary member is:

- absent from the room for part of the meeting; or
- recused from review of certain research protocols because he/she has a conflicting interest with respect to a specific research protocol.

Whenever this occurs, the minutes of the IRB meeting should indicate clearly that the alternate IRB member has replaced the designated primary IRB member. When relevant, OHRP recommends that the reason for the substitution of the alternate IRB member also be documented in the minutes.

In principle, alternate IRB members are fully enfranchised IRB members, requiring education and training, and are held to the same standards as regular members.

D. Recruitment and Retention of IRB Members and Chairpersons

Recruiting individuals who can meet all of the many requirements for research review can present a major obstacle for many institutions. Attempting to create the "perfect" IRB is a challenge that can consume much time for institutional officials, IRB chairpersons, and IRB administrators and is one that has the potential to create a great deal of frustration.

Participation on an IRB by institutional faculty and staff is often considered a component of their job responsibilities as established by their supervisors. However, it is important that institutions recognize individuals for their service on an IRB, as the assignment is often time consuming and is essential to maintaining the research integrity of the institution. In its report, *Responsible Research: A Systems Approach to Protecting Research Participants*, IOM suggested that IRB members should be compensated for their efforts. "This compensation may be monetary, may support academic promotion, or may provide release time from other duties" (2003, 105). Unaffiliated members should, at the very least, receive reimbursement for parking and other miscellaneous expenses.

E. IRB Training, Continuing Education, and Professional Development

Education is an essential feature for developing competence in the ethical review and conduct of research with human subjects (see Chapter 4 for greater detail). Through well-designed, ongoing educational programs, IRB members can learn, for example, the most practical and effective

steps for protecting confidentiality, improving the quality of the informed consent process and its documentation, and addressing issues concerning vulnerable populations. In addition, education programs can help prevent routine ethical issues from becoming needless impediments to research and can provide basic skills to assist investigators and IRB members in dealing with emerging or particularly sensitive ethical issues.

The need for education of IRB members was a major focus of the National Commission, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission), and the Advisory Committee on Human Radiation Experiments (ACHRE). It also was central in NBAC reports.

The National Commission focused on educating IRB members and proposed that the federal government and individual institutions play a role in that effort. The President's Commission recommended a broad educational program targeted to investigators, IRB members, and research administrators, including site visits to institutions by experienced IRB members and administrators (President's Commission 1983). ACHRE highlighted the importance of education by linking the protection of the rights and interests of research participants to the ability of investigators to "appreciate sufficiently the moral aspects of human... research and the value of institutional oversight" (ACHRE 1995). In two of its reports, NBAC recommended that professional associations develop topic-specific educational materials (NBAC 1999; NBAC 1998).

IRB members and others charged with the responsibility for reviewing and approving research should receive detailed training in the regulations, guidelines, and policies that are applicable to human subjects research. Attending workshops and other educational opportunities focused on IRB functions should be encouraged and supported to the extent possible. Training in good research practices and in methods for minimizing risk should be provided. Because research conducted by others may have a bearing on research projects conducted by or at the institution, journals and other research-related materials should be available to staff. Training and continuing education should be documented and added to the records of the IRB.

Several training opportunities exist for IRB members and are described in the following paragraphs:

OHRP's Division of Education and Development (1) produces and coordinates conferences and workshops focusing on issues in human subjects protection (2) promotes cooperative education and development efforts among external groups and consortia to improve human subjects protections and related processes (3) responds to requests for clarification and guidance regarding ethical issues in biomedical and behavioral research involving human subjects (4) provides technical assistance to institutions engaged in DHHS-conducted or DHHS-sponsored research involving human subjects; and (5) maintains, promulgates, and updates educational and institutional review guidance materials.

The National Institutes of Health (NIH) offers a computer-based training course designed for NIH board members that is accessible to the public and required for investigators conducting human research.¹ The Department of Veterans Affairs and the Department of Energy (DOE) provide extensive training materials for their IRBs and investigators.² For example, DOE sponsors a Listserv to provide timely information, news, and the opportunity for dialogue between community IRB members and those interested in the roles and responsibilities of the community member.³

Outside government, organizations such as Public Responsibility in Medicine and Research (PRIM&R) and the Association of American Medical Colleges have traditionally provided education to their constituents. PRIM&R offers an "IRB 101" course before its annual meeting and at the request of institutions throughout the year. In addition, some academic institutions have developed their own courses. Moreover, a Web site is under development to provide a free resource for institutions and individuals interested in education on human subjects protection issues.⁴ The effort is sponsored by the DHHS Office of Research Integrity, DOE, OHRP, and NIH. Although course content is likely to differ among institutions, there is some consensus on the basic elements that should be included.

**Public Responsibility
in Medicine and
Research (PRIM&R)**

In *Responsible Research*, the IOM committee also recommended that specialized training should be offered to IRB members not affiliated with a particular research

¹ See <http://www.cancer.gov/clinicaltrials/learning/page3>.

² See www1.va.gov/oro/page.cfm?pg=116.

³ See www.orau.gov/community/irb/listserv.htm.

⁴ See <http://bioethics.od.nih.gov/researchethics.html> (under development by the Responsible Conduct of Research Education Consortium).

organization and therefore not necessarily familiar with research institutions, research design, and research ethics. Such training could include a description of the process of research, the identities and roles of all who are involved, and the components of a research study; a description of the process within a specific institution, including scientific review and conflicts of interest review; and rules of scientific ethics.

Single focus groups—for example, AIDS and breast cancer patient groups—also offer IRB training to introduce their members to scientific concepts and the research oversight process in order to facilitate their IRB participation.

All members of an IRB should receive continuing education as needed, particularly when new regulatory requirements are issued or new areas of research are increasingly likely to be seen. The IRB administrator should set training and educational requirements and content for IRB members and staff, as well as assure that adequate resources are available for such training and education.

F. IRB Professionals Certification

IRB administrators are now being certified by the Council for Certification of IRB Professionals; through the National Association of IRB Managers; and as Certified IRB Professionals through the Applied Research Ethics National Association in conjunction with the Professional Testing Corporation. These efforts encourage the development of professional staff that can facilitate the ethics review function of the IRB.

G. Liability Insurance

Some groups, including IOM in *Responsible Research* (2003), have recommended that all IRB members (both regular and alternates) should receive liability insurance coverage as part of their IRB membership in their capacity as agents of the institution conducting the research and supporting the IRB.

Key Concepts: IRB Membership

- The effectiveness of the IRB review process depends on the experience and commitment of board members. Reviewers should be able to make complex judgments that depend on an elaborate scientific and intellectual calculus that requires both the ability to assess the ethical appropriateness of the research design and methodology and an awareness of the important elements that affect the ability of potential subjects to refuse or consent to enroll.
- Board members should be especially well grounded in ethics and community values, given their primary function of assessing a scientifically validated protocol in terms of its ethical soundness.
- The Common Rule and FDA regulations at §____.107 and 21 CFR 56.107 require that IRBs must have at least five members, with varying backgrounds, to promote complete and adequate review of research activities commonly conducted by the institution. Board membership must be diverse, representing scientific and nonscientific and institutional and noninstitutional interests.
- No IRB member may participate in the review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
- According to the Common Rule, the IRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. It also must include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
- An IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB.
- A list of current IRB members must be submitted to OHRP or the agency issuing the assurance and also must be retained with the IRB's records. Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of a DHHS-approved assurance.
- All members (both regular and alternates) should receive liability insurance coverage as part of their IRB membership in their capacity as agents of the institution conducting the research and supporting the IRB.
- If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or physically or mentally disabled persons, the IRB must consider the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.
- The IRB chairperson should be a highly respected individual from within or outside the institution, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. Important roles for the IRB chairperson include those of recruiting and evaluating new IRB members.
- Education is an essential feature for developing competence in the ethical conduct of research with human subjects.

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Chapter 8

Institutional Review Board Roles and Authorities

- A. Introduction
- B. Purpose, Scope, and Authority of Institutional Review Boards
- C. Types of Institutional Review Boards
- D. Institutional Review Board Policies and Procedures
- E. Institutional Review Board Review of Cooperative Research
- F. Additional Institutional Review of Institutional Review Board-Approved Research
- G. Reversal of Institutional Review Board Determinations
- H. Institutional Relationships Involving the Institutional Review Board
- I. Institutional Review Board Responsibilities to Oversight Agencies
- J. Institutional Self-Assessment of Human Protection Activities

Key Concepts

References



A. Introduction

This chapter describes the roles and authorities of an Institutional Review Board (IRB). An IRB is a group of persons that has been formally designated by an institution to review research involving human subjects. Depending on institutional policy and the research under review, the IRB may be required to operate in accordance with

1. the Federal Policy for the Protection of Human Subjects, or the Common Rule;¹
2. Department of Health and Human Services (DHHS) human subjects protection regulations at 45 CFR Part 46;²
3. the Food and Drug Administration (FDA) requirements for informed consent and IRB review at 21 CFR Part 50 and Part 56,³ respectively, or other relevant federal agency regulations.

Under some conditions, all three sets of regulations may apply. An example is research on an investigational drug (FDA), sponsored by DHHS (45 CFR 46), being conducted at a Department of Veterans Affairs Medical Center (Common Rule).

Institutions must designate one or more IRBs to review their human subjects research (§____.103(b)(2)); 56 CFR 102(c)(g)). The designated IRB may be operated by the institution itself, by a collaborating or cooperating institution, or by an independent entity. In any case, the institution must acknowledge and accept the scope and authority of its designated IRB as defined in the federal regulations in its federal assurance or in a written agreement or Memorandum of Understanding. The institution may not permit human subjects research that is covered by the federal regulations to go forward without the appropriate review and approval of a designated IRB.

**designated
IRB**

Although an institution's highest officials are ultimately responsible for protecting the dignity, rights, and welfare of its human research subjects, the IRB plays an essential operational role in implementing institutional and regulatory human subjects protection requirements. As such, the IRB acts both as an agent of the institution in protecting human subjects and as the local authority under federal regulations for independent oversight of the institution's human subjects research.

¹ See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm; see 56 *Federal Register* 28003.

² See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

³ See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html and www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html.

Under §____.109(a) and 21 CFR 56.109(a), IRBs are responsible for reviewing human subjects research protocols and have the authority to approve, require modification in (to secure approval), or disapprove research that is covered by the Common Rule or FDA requirements. They also have the responsibility for exercising continuing oversight of all research that they approve. An IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects (§____.113; 21 CFR 56.113).

B. Purpose, Scope, and Authority of IRBs

An IRB's primary purpose is to protect the rights and welfare of subjects involved in human research. To this end, the IRB reviews proposed and ongoing human subjects research to determine that it satisfies basic ethical principles and complies with the requirements of the federal regulations, applicable state law, the institution's federal assurance (if applicable), and the institution's policies and procedures for protecting human subjects.

**prospective
and continuing
review**

The IRB fulfils these responsibilities by conducting prospective and continuing review of human subjects research, including review of:

- the research protocol or research plan and its level of risk versus potential benefits;
- grant applications or proposals for federally supported research involving human subjects;
- the informed consent process;
- the mechanism for documentation of informed consent;
- the procedures used to recruit and enroll subjects;
- advertisements and information sheets for the research;
- data monitoring procedures to ensure subject safety;
- privacy and confidentiality protections;
- safeguards for vulnerable populations of subjects;
- any unanticipated problems involving risks to subjects or others, including adverse events;
- the progress of the research, including the number of subjects enrolled and withdrawn, data monitoring reports, an appropriate summary of adverse events and unanticipated problems involving risks to subjects or others, and relevant multicenter trial reports;
- new findings (inside or outside the research) that may affect the levels of risk and the benefits of the research; and

- new developments (inside or outside the research) that may affect subjects' decisions to participate or to continue participation.

Use of IRBs Required

Whenever an institution becomes engaged in human subjects research to which the Common Rule applies, an IRB that is officially designated under an applicable federal assurance must prospectively review and approve the research, and the institution must certify to the supporting or conducting federal department or agency that the designated IRB reviewed and approved the research. An institution becomes engaged in human subjects research when its employees or agents obtain data through intervention or interaction with living individuals for research purposes or obtain identifiable private information for research purposes (§§____.102(d),(f)). For its human subjects research, FDA defines clinical investigation rather than engagement in research (21 CFR 56.102(c); (see below).

If subject to the Common Rule (i.e., the research is not exempt), human subjects research meeting any *one* of the following criteria must be prospectively reviewed and approved by an institutionally designated IRB:

- research conducted by an employee or agent of the institution
- research taking place within an institutional facility
- research utilizing institutional resources
- research sponsored by the institution
- research accessing identifiable private information held by the institution

Approval to rely on an IRB that is not designated in an institutional assurance requires that all three of the following criteria be met:

- written permission of the institution's human subject signatory official
- a written agreement signed by an appropriate official of the organization operating the IRB
- modification of the institution's federal assurance to designate the IRB for the research involved

FDA requires IRB review (except as provided in §56.104 and §56.105) for clinical investigations of FDA-regulated test articles. FDA may decide not to consider supporting an application for a research or marketing permit or any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB. A determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant of any obligation under any

other applicable regulations (e.g., the Common Rule) (see also Chapter 3 for a description of differences among the regulatory requirements).

Prospective and Continuing IRB Review and Approval Required

No human subjects research may be initiated, modified, or continued beyond a certain period established by the IRB without the prospective approval of a designated IRB. The requirement for prospective review and approval of proposed research and of proposed changes to approved research, as well as the requirement for periodic continuing review and approval of ongoing research at intervals appropriate to the degree of risk (but not less than once per year), is intended to ensure that subjects' rights and welfare are protected throughout the course of the research (§____.109(e); 21 CFR 56.109(f)).

Authority to Observe or Monitor Research

An IRB has the authority to observe or have a third party observe the informed consent process and the research to whatever extent it considers necessary to protect human subjects and ensure compliance with applicable laws, regulations, and policies (§____.109(e); 21 CFR 56.109(f)).

Authority to Take Action

The IRB has the authority to approve, require modifications in (to secure initial or continuing approval), or disapprove research covered by the Common Rule or FDA regulations (§____.109(a); 21 CFR 56.109(a)). In order to ensure protections for subjects, the IRB may require the following modifications to secure approval:

- that a research project undergo major revisions;
- that the applicable consent document be extensively revised;
- that an investigator from a particular research project be removed;
- or that an investigator complete education and training in the ethics and regulation of human subjects research;
- that any other reasonable measure deemed appropriate by the IRB be taken to protect the rights and welfare of human research subjects.

Authority to Suspend or Terminate Research Activities

The IRB has authority to suspend or terminate approval of research that is not being conducted in accordance with

the IRB's requirements or that has been associated with unexpected serious harm to subjects (§____.113; 21 CFR 56.113).

C. Types of IRBs

IRBs may be operated by institutions that conduct human subjects research or independent organizations that do not conduct human research. FDA and the DHHS Office for Human Research Protections (OHRP) recognize both types of IRBs. Contractual IRB arrangements can be established with either stand-alone IRBs or with those at another institution.

Although review by a local IRB historically has been the preferred approach, there has been increasing recognition that there may be circumstances in which local review is not always necessary or appropriate. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission), which strongly supported a system of local IRBs, has recognized that in some cases research studies did not require review by an IRB located in or near the institution where the research would be conducted. For small institutions, other arrangements, such as the use of another institution's IRB or several institutions forming a joint IRB, were considered acceptable by the National Commission (National Commission 1979).

**local review
is not always
necessary or
appropriate**

Although IRBs must have adequate knowledge of the local research context, there are no regulatory requirements that preclude review by IRBs that are not organizationally part of the institutions conducting research and/or are not geographically close to the research site. What is required is that the IRB should have sufficient knowledge of the local research context—in terms of the relevant institutions, the relevant investigators, and the relevant communities—to conduct an effective review (§____.103(d), §____.107(a), §____.111(a)(3), (4), (7), (b), §____.116). In 1981 FDA affirmed the acceptability of nonlocal review of research (review by an IRB geographically remote from the research site and/or independent of the institution conducting the research), as long as the IRB obtains sufficient knowledge of the local research context (21 CFR 56.107, 56.111(a)(3), 56.111(a)(7), 56.111(b); FDA 1998, 19-20). (see Chapter 15 for a discussion of central IRBs).

In recent years, guidance from OHRP has also moved in this direction. OHRP allows "institutional sites that are geographically close enough to comfortably contribute membership to a common IRB" to create such a shared, or

⁴ See www.hhs.gov/ohrp/humansubjects/guidance/irb-rely.htm.

common, IRB.⁴ In addition, OHRP has approved assurances in which an institution designated an independent IRB that was geographically distant from the institution (e.g., a central

local research context

IRB). In these cases, the IRB should demonstrate that it has obtained the necessary information about the local research context through one or more

of the following mechanisms or through other mechanisms deemed appropriate by OHRP for the proposed research and the local research context:

- personal knowledge of the local research context on the part of one or more IRB members, with such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community
- participation (either physically or through audiovisual or telephone conference) by one or more appropriate consultants in convened meetings of the IRB, such consultant(s) having personal knowledge of the local research context and such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community

Regardless of whether a local or central IRB is used, an institution conducting research is responsible for protecting the rights and welfare of the research subjects in all research over which it has review and approval authority.

D. IRB Policies and Procedures

Institutions and IRBs that are bound by the Common Rule must have and follow written policies and procedures for:

- conducting the initial review of research
- conducting continuing review of research
- reporting its findings and actions regarding initial and continuing review to investigators and the institution
- determining which projects require review more often than annually
- determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review
- ensuring prompt reporting to the IRB of proposed changes in research activity
- ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject

- ensuring prompt reporting to the IRB, appropriate institutional officials, and appropriate federal officials of:
 - any unanticipated problems involving risks to subjects or others
 - any serious or continuing noncompliance with regulatory requirements or the requirements or determinations of the IRB, OR
 - any suspension or termination of IRB approval (§____.103(b)(4),(5) and §____.108(a); 21 CFR 56.108)

Both OHRP and FDA have required that IRBs maintain comprehensive written operating procedures for each of the items listed above (see Chapter 9 for information on IRB administration).

E. IRB Review of Cooperative Research

Institutional policy should specify the IRB review requirements for cooperative research, particularly in cases where special IRB review arrangements have been developed. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with §____.114 (see Chapter 15 for an extensive discussion of cooperative research).

joint IRB review arrangements

With the approval of the appropriate federal department or agency head or his/her designee, institutions are permitted to enter into joint IRB review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort (§____.114).

Any IRB that an institution uses for the review of its research that is covered by the Common Rule must be designated under the institution's federal assurance. If the IRB is not operated by the institution, a written agreement must detail the respective responsibilities of the institution and the organization that operates the IRB.

Designation of One Institution's IRBs Under Another Institution's Assurance

If a designated IRB is not operated by the institution holding the assurance, a written agreement must detail the respective responsibilities of the institution and the institution or organization that operates the IRB. This written agreement must be signed by each institution or organization. IRBs can have no authority or responsibility under another institution's federal assurance without such a written agreement.

Review of Research Involving Noninstitutional Investigators

Any review by an institutional IRB of research involving an individual who is not an employee or agent of the institution (e.g., private practitioner), regardless of the location of the research, should be accompanied by a written agreement specifying the responsibilities of the noninstitutional investigator.

Review of Noninstitutional Research

Noninstitutional research is research that does not meet at least *one* of the following criteria:

- human research conducted by an employee or agent of an institution
- human research taking place within an institutional facility
- human research utilizing institutional resources
- human research sponsored by an institution
- human research accessing identifiable private information held by an institution

IRBs cannot accept responsibility for the review and oversight of noninstitutional research without the written agreement of their institutional human subject signatory official and of the corresponding official at the institution engaged in the research.

F. Additional Institutional Review of IRB-Approved Research

An institution maintains the prerogative not to conduct research that has been approved by its designated IRBs. Despite IRB approval, an institution may determine that the research will not be conducted or supported by the institution for any reason (§____.112).

Some of the more common reasons that an institution might decline to conduct IRB-approved research include the following:

- A satisfactory contractual agreement could not be concluded with the industry sponsor.
- The research would require resources that the institution could not provide.
- The research would not be consistent with the institution's mission or values.
- The research would expose the institution to unacceptable liability.

- The research would expose the institution to undesirable publicity or damage its public image.

G. Reversal of IRB Determinations

No institutional official or institutional committee may set aside or overrule a determination by an institutionally designated IRB to disapprove research or to require modifications to secure approval for proposed research under its oversight (§____.112).

Notice to Investigator of Disapproval

An IRB must provide the research investigator with a written notification of its decision to disapprove research or of modifications required to secure the approval of proposed research. If the IRB decides to disapprove research, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing (§____.109(d)).

Investigator Response and Resubmission

In reaching its determinations, an IRB must carefully and fairly evaluate the investigator's response to any determination disapproving or requiring modifications in the proposed research. There is no regulatory limit to the number of times a research project can be revised and resubmitted to the IRB for consideration.

H. Institutional Relationships Involving the IRB

As discussed in Chapter 1, the ethical conduct of research is an individual, organizational, and shared responsibility. Although protecting human subjects is the personal responsibility of every individual involved in the research process, no single person can ensure that subjects are protected in every research project. Consequently, organizations involved in research have an explicit responsibility to establish and maintain effective systems to protect human subjects.

Human Subject Signatory Official

Under the Common Rule, the institution's human subject signatory official on a federal assurance of compliance is responsible for ensuring appropriate review and oversight of the institution's human research protection program (HRPP) and its systemic protections for human subjects. This review and oversight responsibility may require reviewing IRB policies and procedures and auditing

IRB files, subject records, investigator research files, or regulatory materials maintained by investigators and their staff.

Relative to the IRB, the signatory official's review and oversight responsibilities might include the following:

- designating one or more IRBs to be responsible for the oversight of human subjects research under the institution's federal assurance
- ensuring that the institution's IRBs are provided with sufficient staff, resources, and physical space to support their review and record-keeping responsibilities
- ensuring that the institution's IRB members and staff, and other relevant personnel, are educated regarding human subjects protection requirements
- monitoring to ensure IRB compliance with federal, state, and local regulatory requirements and with the institution's federal assurance
- preparing reports of oversight activities and findings for submission to the institution's chief executive, compliance officer, legal counsel, and IRB
- requiring corrective actions to address deficiencies
- participating in regulatory inquiries and/or corresponding with regulatory authorities concerning the protection of human research subjects

IRB Reporting to the Human Subject Signatory Official

Institutional policy should ensure that designated IRBs:

- provide, at regular intervals, to the institutional human subject signatory official with a substantive report of their activities and concerns
- report to the signatory official any serious unanticipated problems involving risks to subjects or others
- provide the institutional human subject signatory official with copies of any reports or correspondence to or from any federal, state, or local regulatory agency

IRB Access to Institutional Officials

Institutional policy should ensure that its designated IRBs, or any member of a designated IRB, can bring any matter directly to the attention of the institution's human subject signatory official, compliance officer, legal counsel, or chief executive, when warranted.

IRB Access to Regulatory Correspondence

Institutional policy should ensure that all individuals subject to IRB oversight, including investigators and their staff, are required to provide the relevant IRB (and the institution's human subjects assurance signatory official) with copies of any correspondence, inspection reports, or audit findings to or from any federal, state, or local regulatory agency that bear upon the protection of human subjects.

Access to Sponsor Correspondence

Institutional policy should ensure that all individuals subject to IRB oversight, including investigators and their staff, are required to provide the relevant IRBs (and the institution's human subject signatory official) with copies of any correspondence, monitoring reports, or audit findings to or from the research sponsor (or agents of the research sponsor) that bear upon the protection of human subjects.

Relationship of an IRB to the Research Sponsor

The Principal Investigator is usually responsible for acting as the communications link between an IRB and the sponsor of the research. However, an IRB may communicate directly with the sponsor when the IRB deems such communication to be warranted. The FDA device regulations require direct sponsor-IRB communication under specific circumstances. (See 21 CFR 812.66 and 812.150(b)(1).)

I. IRB Responsibilities to Oversight Agencies

Written institutional policy must clearly describe an IRB's responsibilities relative to federal, state, and local oversight agencies.

Reporting to Oversight Agencies

Written institutional policy must clearly describe the specific, operational responsibilities of the human subject signatory official and the institution's designated IRBs for reporting:

- unanticipated problems that involve risks to subjects or others

- serious or continuing noncompliance with the common Rule, FDA regulations, or IRB determination or requirements for protecting human subjects
- suspension or termination of IRB approval of research to appropriate federal agencies
- although the signatory official is responsible for ensuring reporting to federal officials under the institution's federal assurance, this responsibility may be delegated to the IRB chairperson or to another institutional official as long as the delegation is clearly described in writing.

Prerogatives of the IRB

Institutional policy should make clear that the IRB chairperson and IRB members have the authority and responsibility to contact relevant federal regulatory officials about matters relating to the protection of human subjects in research. Institutional policy should provide specific protections for IRB members and others who, acting in good faith, report possible violations of human protection requirements to institutional officials or federal regulators.

J. Institutional Self-Assessment of Human Protection Activities

One responsibility of the human subject signatory official is the periodic assessment of the effectiveness of an institution's HRPP. This assessment may be solely an internal undertaking, or it may involve review by outside experts (see Chapter 23 for a more extensive discussion of audits, self-assessments, and accreditation).

Several tools that can be used for institutional self-assessment of human subjects protection activities are now available free of charge on the Web:

- **OHRP Quality Improvement Program**
OHRP offers quality assessment, instruction, education, and best practices information to HRPPs on a voluntary basis.⁵ For example, OHRP offers a guided self-assessment to help organizations develop a solid foundation for a human subjects protection program (see Chapter 4 for further discussion).

- **FDA Materials**

FDA (1998) has on its Web site a checklist entitled *A Self Assessment Checklist for IRBs*,⁶ which provides an inventory of policies and procedures required by FDA and that the IRB could consider adopting.

- **Association for the Accreditation of Human Research Protection Programs Evaluation Instrument**

The Association for the Accreditation of Human Research Protection Programs (AAHRPP) has posted on its Web site the detailed evaluation instrument used by AAHRPP accreditation site visitors.⁷ This instrument contains the specific indicators that site visitors look for in determining whether applicant programs have satisfied the accreditation standards and elements. It can easily be adapted by an institution to perform a thorough self-assessment of its institutional HRPP.

- **Partnership for Human Research Protection, Inc., Accreditation Programs**

The Partnership for Human Research Protection (PHRP) is a joint venture of the Joint Commission on Accreditation of Healthcare Organizations and the National Committee for Quality Assurance.⁸ PHRP offers two accreditation programs: one for organizations that conduct human research and one for independent review boards that review research but do not themselves conduct research. The standards address both of these accreditation options and could be adapted by an institution to perform a self-assessment.

⁵ See www.hhs.gov/ohrp/humansubjects/qip/qip.htm.

⁶ See www.fda.gov/oc/ohrt/irbs/irbchecklist.html.

⁷ See [www.aahrpp.org/www.aspx?PageID=25\\$12](http://www.aahrpp.org/www.aspx?PageID=25$12).

⁸ See www.phrp.org/.

Key Concepts: Institutional Review Board Roles and Authorities

- An IRB is a group of persons that has been formally designated by an institution to review research involving human subjects.
- An IRB's primary purpose is to protect the rights and welfare of human subjects involved in research.
- An IRB may be operated by the institution conducting the research, by a collaborating or cooperating institution, or by an independent entity.
- The IRB acts both as an agent of the institution in protecting human subjects and as the local authority under federal regulations for independent oversight of the institution's human subjects research.
- No nonexempt human subjects research covered by the Common Rule or FDA regulations may be initiated, modified, or continued without prospective and ongoing approval of the institution's designated IRB.
- The IRB has authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.
- The IRB has the authority to observe or have a third party observe the research under its oversight.
- The IRB has the authority to observe or have a third party observe the informed consent process.
- The IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects in research under its oversight.
- The Common Rule, DHHS regulations, and FDA regulations require that IRBs follow written policies and procedures.
- Joint IRB review arrangements, reliance upon the review of another qualified IRB, and arrangements to avoid duplication of effort require written agreements that specify the responsibilities of each party.
- An institution maintains the prerogative to not conduct research that has been approved by its designated IRBs.
- No institutional official or institutional committee may set aside or overrule a determination by an institutionally designated IRB to disapprove research or require modifications in research under its oversight.
- An IRB must provide the research investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the investigator an opportunity to respond in person or in writing.
- Institutional policy should ensure that all individuals subject to IRB oversight are required to provide the relevant IRB (and the institution's human subject signatory official) with copies of any correspondence, inspection reports, monitoring reports, or audit findings to or from any regulatory agency or sponsor that bear upon the protection of human subjects.
- The IRB may communicate directly with the sponsor when the IRB deems such communication to be warranted or when the FDA device regulations require it.
- Written institutional policy must clearly describe the specific, operational responsibilities of the human subject signatory official and the institution's designated IRBs for reporting (1) unanticipated problems involving risks to subjects or others; (2) serious or continuing noncompliance with federal, institutional, or IRB requirements for protecting human subjects; and (3) suspension or termination of IRB approval of research to federal agencies.
- One responsibility of the human subject signatory official is the periodic assessment of the effectiveness of an institution's HRPP.

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Chapter 9

Administration of Institutional Review Boards

- A. Introduction
 - B. The Centrality of the Institutional Review Board
 - C. Institutional Commitment
 - D. Institutional Review Board Staffing
 - E. Record Keeping and Required Documentation
 - F. Record Retention and Access
 - G. Protocol Tracking
- Key Concepts**
References



A. Introduction

Many individuals and institutions share responsibility for the protection of research subjects. Collectively, these parties form human research protection programs (HRPPs). These programs can be extremely large in some institutions, particularly those that perform a high volume of research. In most organizations the HRPP includes Institutional Review Boards (IRBs), the investigators and staff who actually conduct the research, the department/office/individuals responsible for meeting the obligations imposed by the assurance of compliance with the regulations, and the research sites (see Chapter 1). Depending on the type of research being conducted, other groups, entities, committees, or departments also could be considered part of an HRPP. However, the form that an actual HRPP takes and the roles assigned to its various components are less important than its comprehensiveness and level of accountability. Although each institution with an HRPP is likely to use slightly varied titles and have different duty descriptions and lines of communication, each should have a well-designed and appropriately resourced infrastructure for protecting research subjects.

Ideally, an HRPP operates to maximize the protection of research subjects while minimizing unproductive administrative activities and excessive costs (IOM 2003). Although

substantive ethical principles and standards should govern behavior, it is important to recognize that excessive focus on the procedural aspects of IRB activities can obscure the primacy of these ethical principles. Nonetheless, the Common Rule ultimately holds IRBs primarily responsible for ensuring that proper procedure is followed and that documentation is complete and correct.

The Office for Human Research Protection's (OHRP's) compliance activities¹ reflect this emphasis on the regulations by focusing on ensuring that the procedures by which protocols are reviewed are appropriate—for example, that proper exempt and expedited procedures be adhered to, requirements for quorum are fully met, annual review is conducted at appropriate intervals, and all findings and votes of the IRB are properly recorded.

This chapter focuses on the significant administrative responsibilities and recordkeeping requirements of the IRB and its key staff, with the understanding that meeting these requirements does not, in and of itself, guarantee that human subjects are fully protected under the law.

¹ See <http://www.hhs.gov/ohrp/compliance/index.html>.

B. The Centrality of the IRB

The ethical and administrative focus of most HRPPs tends to be the IRB. The Common Rule at §_____.103(b)(4) and Food and Drug Administration (FDA) regulations at 21CFR §56.108(b) require that an institution and/or IRB implement written policies and procedures to govern the operations and direct the activities of the IRBs responsible for reviewing research at that institution. Typically, IRB standard operating procedures (SOPs) documents, which establish how policies and procedures are to be followed in practice, satisfy this requirement. SOPs and written policies and procedures also can be the focus of scrutiny on the part of accrediting institutions (see Chapter 23).

The IRB's role, function and operation are delineated in federal regulations, which provide the blueprint for its administrative responsibilities.

The Common Rule and applicable FDA regulations specify as follows how the IRB should conduct its business:

the IRB must have sufficient resources

- The IRB must have sufficient resources (meeting space and staff) to support its review and recordkeeping duties (§____.103 (b)(2)).
- The IRB must have written procedures for:
 - conducting initial and continuing review of research
 - reporting its findings and actions to the investigator and the institution
 - determining which projects require review more often than annually
 - determining which projects need verification from sources other than investigators that no material changes have occurred since the previous IRB review
 - ensuring prompt reporting to the IRB of changes in research activity
 - ensuring that proposed changes in approved research that are made during the approval period are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects (§____.103(b)(4); 21 CFR 56.108(a))
- The IRB must have written procedures for ensuring the prompt reporting of:
 - any unanticipated problems involving risks to subjects or others
 - any serious or continuing noncompliance with the federal regulations
 - any serious or continuing noncompliance with the requirements or determinations of the IRB, and
 - any suspension or termination of IRB approval (§____.103(b)(5); 21 CFR 56.108(b))
- The IRB must have membership that conforms to the regulations (§____.107; 21 CFR 56.107).
- The IRB must review research in compliance with the regulations, including:
 - having the authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by the regulations
 - requiring that information given as part of informed consent be provided in accordance with regulations
 - requiring information in addition to that required by the regulations be given to subjects if the IRB judges that it
 - providing written notification of IRB decisions
 - providing written statements of reasons for the disapproval of research and giving the investigator an opportunity to respond
 - determining the frequency of continuing review, appropriate to the degree of risk
 - having the authority to observe or have a third party observe the consent process and the research (§____.107(e); 21 CFR 56.109(f)).
- The IRB must meet the following specific criteria to approve research (§____.111; 21 CFR 56.111):
 - risks must be minimized and reasonable in relation to anticipated benefits
 - equitable selection of subjects must be ensured
 - informed consent must be sought in accordance with and to the extent required by §____.116 and 21 CFR 56.116
 - informed consent must be appropriately documented in accordance with and to the extent required by §____.117 and 21 CFR 50.27
 - the research plan must make adequate provision for monitoring data to ensure subject safety (when appropriate)
 - adequate provisions must be in place to protect subject privacy and maintain data confidentiality (when appropriate)
 - additional safeguards must be in place to protect the rights and welfare of vulnerable subjects (if needed)
- The IRB must have the authority to suspend research (§____.113; 21 CFR 56.113).
- The IRB must prepare and maintain records of its activities as specified in the regulations (§____.115; 21 CFR 56.115), including the following:
 - files on research proposals that contain copies of the proposal reviewed, scientific evaluations (if any) accompanying the proposals, approved sample consent documents, progress reports from investigators, and reports of injuries to subjects
 - minutes of IRB meetings in sufficient detail to show meeting attendance, actions taken by the IRB votes on actions (including those for, against, and abstaining), the basis for requiring changes in or disapproval

ing the research, and written summaries of controverted issues and their resolution

- records of continuing review activities
 - copies of all correspondence between the IRB and investigators
 - a list (roster) of IRB members, including information required by §_____.103(b)(5) and 21 CFR 56.115(a)(5)
 - written procedures as described at §_____.103(b)(4) and §_____.103(b)(5) and 21 CFR 56.108(a) and (b)
 - statements of significant new findings as required by §_____.116(b)(5) and 21 CFR 50.25, and
 - records required by regulations relating to research and that must be retained for at least three years after the research is completed
- For IRBs that review research involving FDA-regulated investigational devices, as part of an abbreviated Investigational Device Exemption (IDE) application, the IRB also may have to determine whether the device is a significant or nonsignificant risk device (21 CFR 812.2(b))

An IRB does not function in isolation but rather is central to and a crucial element of an HRPP. If the IRB is not functioning properly, it can be said that the HRPP also is not functioning properly. This means that the IRB must have the resources to conduct more than the day-to-day administrative responsibilities of a single committee; it also must have the resources to support its activities as the pivotal body that works with their entities within an HRPP. Many IRBs have been given other responsibilities in addition to the oversight of human subjects protection, including providing education (of IRB members/staff and investigators) and overseeing investigator compliance with the human subjects protection regulations. The IRB often is considered the logical entity for conducting these activities, in addition to maintaining records that conform to the regulatory standards, which means that many IRBs are required to maintain extra or special records and communicate widely across an HRPP. For these reasons, when assessing the level of administrative support needed and allocating resources, an IRB generally cannot be compared with other institutional committees. Instead, an IRB must be assessed separately, with special attention given to how it must function to fulfill its regulatory responsibilities and its role within an HRPP.

C. Institutional Commitment

The regulatory functions of an IRB require that it has the authority to perform its mandated functions and sufficient resources to support all of the activities required by the regulations. An IRB must be in complete compliance with the applicable regulations—“almost” or “close” is not only insufficient, it is considered noncompliant and could become grounds for regulatory action.

**complete
compliance with
the applicable
regulations**

Because regulatory noncompliance is the underlying issue, it is important that an IRB obtain adequate managerial and administrative support to function in compliance with the regulations. Most importantly, the institution’s leadership must support the authority of the IRB and provide the necessary resources, such as adequate staffing and space, to fulfill its regulatory responsibilities. The Common Rule at §_____.16.103(b)(2) requires research institutions to provide their IRBs sufficient staff and meeting space to support their review and recordkeeping responsibilities. Providing the resources needed to establish and maintain the administrative infrastructure necessary for a robust HRPP is the responsibility of the research institution and the research sponsor (IOM 2003).

In addition, IRBs have extensive recordkeeping requirements, underlining the importance of adequate administrative support. These requirements go beyond simple documentation of IRB functions, because the records can serve as evidence of compliance. Not all other institutional committees operate under such rigid constraints.

Adherence to administrative requirements is most likely to occur if sufficient resources (e.g., staff, budget) have been allocated by an institution to its HRPP. However, a lack of adequate resources has been noted in some OHRP site visits. In addition, a report commissioned by the National Institutes of Health (NIH) in the late 1990s, *Reducing Regulatory Burden*, noted that, despite increasing IRB workloads, resources available to IRBs were decreasing. This report recommended providing additional federal resources when adding to IRB duties (Mahoney 1999).

Different factors can contribute to how an institution supports the authority of an IRB. For example, clear institutional policies should be in place that describe its authority and any actions that are necessary to enforce these policies. The institution also must be willing to back up an IRB’s enforcement actions, if necessary, because, if an institution does not support an IRB’s regulatory responsibilities, outside regulatory agencies may intervene and impose sanctions.

Another important factor in maintaining an IRB’s authority is how it is placed within the institution. An IRB should be able to act to approve research independently of institutional pressures. If an IRB is placed within a research administration office, for example, it could be in the position of apparent conflict of interest and potential loss of independence. An IRB must be willing and able to refuse to approve research that poses unacceptable risks of harm to subjects without being pressured by those involved in the administrative aspects of research to approve a well-funded study. This potential conflict also can exist when the IRB administrator/manager is supervised by a research administration office, which, again, can influence an IRB administrator’s ability to act independently.

In such situations, even when such pressure is not exerted at an institution, the potential for and the perception of such a conflict can remain.

D. IRB Staffing

IRBs are responsible for documenting their actions and determinations to ensure that they fully satisfy all regulatory requirements. They also may be responsible for educating IRB members, investigators, study coordinators, and other members of the research community through both formal training programs and routine day-to-day interactions regarding specific research proposals or human subjects protection issues. Thus, IRB staff should have a detailed working knowledge of accepted ethical principles, relevant regulatory requirements, and institutional policies and procedures. To ensure that IRB support staff members function successfully, they must receive initial and continuing education on human subjects protection requirements (see Chapter 4).

The staffing requirements of an IRB will vary with its volume of work. For a medium-volume facility with one or two IRBs, staff might include an IRB administrator/manager, an administrative assistant, a computer analyst (or centralized computer support), and several individuals who review protocols. A high-volume facility obviously will need more staff members to ensure optimal performance. A small-volume facility would have fewer staffing requirements, but the regulatory requirements for keeping records and documenting the IRB's actions require that at least one staff member has clear responsibility for overall IRB operations.

IRB Administrator/Manager Duties

Various titles that might be used for the individual charged with overall IRB operation include human subjects protections administrator, IRB coordinator, IRB administrator, IRB manager, or IRB clerk. Although the duties of the IRB administrator/manager may vary from institution to institution, they should be clearly defined in a position description or scope of duties document. In general, the IRB administrator/manager is responsible for the following:

- directing and overseeing all IRB support functions and operations
- training, supervising, and evaluating IRB staff
- developing and implementing procedures to effect efficient document flow and maintenance of all IRB records
- verifying exemptions on behalf of the research institution

- maintaining the official roster of IRB members
- developing the budget and accounting for expenses
- scheduling IRB meetings
- distributing pre-meeting materials
- compiling the minutes of IRB meetings (see below) in compliance with regulatory requirements
- promptly reporting changes in IRB membership to OHRP or to the agency granting the assurance
- maintaining all IRB documentation and records in accordance with regulatory requirements
- assisting new IRB members in completing orientation procedures and meeting required education standards
- ensuring that all IRB records are secured and properly archived
- facilitating communication between investigators and the IRB
- tracking the progress of each research protocol submitted to the IRB
- maintaining a database for tracking purposes (computerized if necessary)
- serving as a resource for investigators on general regulatory information and providing guidance about forms and submission procedures
- training research investigators and staff
- maintaining training documentation and reference materials related to human subjects protection requirements
- maintaining and updating the IRB investigators' manual and IRB forms
- drafting reports and correspondence to research investigators on behalf of the IRB or IRB chairperson regarding the status of the research, including conditions for approval of research and cases of adverse events or unanticipated problems
- drafting reports and correspondence directed to research facility officials, federal officials, and others on behalf of the IRB or IRB chairperson
- maintaining quality control of IRB support functions
- assisting in evaluating, auditing, and monitoring human subjects research as directed by the IRB or other institutional officials
- keeping manuals and SOPs up to date
- assisting with accreditation visits, if applicable
- coordinating and assisting during regulatory inspections and site visits

In addition to these tasks, the IRB administrator/manager must consult with the IRB chairperson on matters related to membership, meeting conduct, and review of research.

E. Record Keeping and Required Documentation

The Common Rule at §_____.115 and FDA regulations at 21 CFR 56.115 require that institutions or, when appropriate, an IRB prepare and maintain adequate documentation of IRB activities. A large amount of information must be stored and kept current, as listed in Table 9.1.

Written Operating Procedures for the IRB

As a condition of its assurance, the IRB must maintain on file its written procedures for:

- conducting its initial and continuing review of research and reporting its findings and actions to the investigator and the institution
- determining which projects require review more than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review
- ensuring prompt reporting to the IRB of proposed changes in a research activity and ensuring that such changes in approved research, during the period for which IRB approval has already been given, are not initiated without IRB review and approval, except when needed to eliminate apparent immediate hazards to subjects (§_____.103(b)(4))

The IRB also must have on file its written procedures for ensuring the prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of the following:

- any unanticipated problems involving risks to subjects or others and any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB, and
- any suspension or termination of IRB approval (§_____.103(b)(5); 21 CFR 56.113)

IRB Membership Rosters

The IRB administrator/manager should ensure that current IRB membership rosters are maintained and that any changes in IRB membership are reported promptly by the IRB administrator/manager to OHRP or the agency granting the assurance. The roster must be on file with OHRP or the relevant agency at all times and must be consistent with requirements of §_____.103(b)(3). The roster must include a list of IRB members identified by the following:

- name
- earned degrees
- representative capacity (e.g., regular member, nonaffiliated)
- indications of experience, such as board certifications and licenses that describe the member's chief anticipated contributions to IRB deliberations
- any employment or other relationship between the member and the institution (e.g., full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant)

Table 9.1 IRB Records

Generally, IRB records should include files organized into the following categories:

- Written operating procedures
- IRB membership rosters
- IRB research application (protocol) files
- Documentation of convened IRB meetings—minutes
- Documentation of exemptions
- Documentation of expedited reviews
- Documentation of review by another institution's IRB, when appropriate
- Official IRB correspondence and communications
- Documentation of cooperative review agreements, for example, memoranda of understanding
- Federalwide Project Assurance
- Serious adverse event reports
- Education and training records

Copies of All Research Proposals Reviewed

Documentation of research protocols should include any scientific evaluations that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects (see Protocol Tracking below).

The complete documents received from the investigator, including the protocol, the investigator's brochure, a sample consent document, and any advertising or recruitment material intended to be seen or heard by prospective study subjects, should be reviewed. In addition, investigators might be required to submit the following for the record:

- a financial disclosure statement
- FDA Form 1572 for an Investigational New Drug application or a signed investigator agreement for an Investigational Device Exemption (IDE), if applicable
- documentation that the study has been reviewed and approved by other committees charged with the oversight of research at the institution (e.g., conflict of interest board, Privacy Board, scientific review committee, safety board).

Some IRBs also require the investigator to submit an institutionally developed protocol summary form. When the IRB makes changes, such as in the wording of the informed consent document, only the final approved copy needs to be retained in the IRB records.

Documentation of Convened IRB Meetings—Minutes

The Common Rule at §____.115(a)(2) and FDA regulations at 21 CFR 56.115(a)(2) require that an IRB prepare and maintain adequate documentation of "minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution."

However, these requirements are minimal. Minutes should enable a reader who was not present at the meeting to determine exactly how and with what justification the IRB arrived at its decisions. Minutes should include the following:

1. Attendance by name (members present, members absent, names of alternates in lieu of specified absent members, consultants present, investigators present, guests present). Attendance should reflect who was present and absent for the discussion of and vote on each protocol.

2. Actions that might be taken by the convened IRB on each agenda item that requires full IRB action, which include the following:
 - a. Approved with no changes (or no additional changes). The research may proceed.
 - b. Approvable with minor changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so that the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol is approved by the designated reviewer using an expedited review procedure.
 - c. Approvable with substantive changes that must be reviewed at a convened IRB meeting. The research may proceed only after the convened IRB has reviewed and approved the required changes.
 - d. Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information regarding the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application that incorporates all of the necessary information.
 - e. Disapproved. The IRB has determined that the research cannot be conducted at the facility or by employees or agents of the facility.

Each determination should include voting results, including the number for and against, any abstentions, and members who recused themselves and the reasons for recusal. It should also include the basis for requiring changes in or disapproving research. This information should be provided in writing to the investigator, who should be given an opportunity to respond in person or in writing.

3. A written summary of discussion of all controverted issues and their resolutions. This might include, for example, specific measures taken to protect vulnerable populations; review of protocol or informed consent modifications or amendments; unanticipated problems that involve risks to subjects or others; adverse event reports; reports from sponsors, cooperative groups, or Data and Safety Monitoring Boards (DSMBs); reports of continuing noncompliance with the regulations or IRB determinations; waivers or alterations of elements of informed consent and justification; suspensions or terminations of research; and other actions.
4. IRB minutes also might reflect a list of research approved since the last meeting, utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol.

Draft minutes of an IRB meeting should be distributed to IRB members at the next meeting for review and approval.

More on IRB Findings and Determinations for Which Documentation Is Required by Regulation

Although the regulatory agencies agree on the IRB functions and actions that must be documented, the methods of documentation are not regulated and have been the subject of varying guidance. OHRP guidance provides that the following specific IRB findings and determinations should be documented in IRB meeting minutes:

1. The level of risk of the research
2. The approval period for the research, including identification of research that warrants review more often than (at least) annually
3. Identification of any research for which verification is needed from sources other than the investigator that no material changes have been made in the research (e.g., cooperative studies or other collaborative research)
4. Justification for waiver or alteration of informed consent, addressing each of the four criteria at §____.16.116(d) (this cannot be done if an FDA test article is involved) The FDA does not permit waiver of documentation. Obtaining informed consent is “deemed feasible” except in two situations (clinical emergency and emergency research. 21 CFR 50.23, 50.24. In addition, exceptions to informed consent requirements 21 CFR 50.23:
 - Subject is confronted with life-threatening situation necessitating use of test article
 - Informed consent not possible because of an inability to communicate with, or obtain legally effective IC from the subject
 - No time to obtain consent from LAR
 - No alternative method of approved therapy available that provides equal or greater likelihood of saving subject’s life
 - IRB approves emergency research without requiring IC.
5. Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at §____.16.117(c)
6. For institutions that have signed on to Subpart B for the purposes of conducting Department of Health and Human Services (DHHS)-supported research, justification for approval of research involving pregnant women and human fetuses, addressing each of the criteria specified under 45 CFR 46 Subpart B of the DHHS human subjects regulations.
7. For DHHS-supported research, justification for approval of research that involves prisoners, addressing each of the categories and criteria specified under 45 CFR 46 Subpart C of the DHHS human subjects regulations. Generally, the IRB administrator/manager is responsible for providing certification of an IRB’s findings to OHRP.

8. For research conducted or supported by DHHS, the Department of Veteran’s Affairs (VA), and the Department of Education and for FDA-regulated research, justification for approval of research that involves children, addressing each of the categories and criteria specified under 45 CFR 46 Subpart D of the DHHS and FDA human subjects regulations, is required. VA policy specifies that a waiver for research that involves children must be obtained from the Chief Officer, Research and Development Office (Veterans Health Administration Directive 2001-028, April 27, 2001). Generally, the IRB administrator/manager is responsible for providing notification to OHRP of the IRB’s findings concerning research requiring review by a panel of experts convened in accordance with Subpart D. For FDA-regulated research, documentation of the IRB findings is required. Notification should be provided to the Commissioner of FDA.
9. Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, co-workers, or economically or educationally disadvantaged persons, regardless of the source of support for the research, and
10. Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24.

Institutions should review the OHRP guidance and tailor the model to their needs, if allowable. FDA guidance allows certain findings to be documented in other formats, such as reviewer checklists that are filed in the protocol files. FDA requires that these other methods be approved by the IRB and outlined in the IRB procedures.

Records of Continuing Review Activities

After an IRB approves a study, continuing review should be performed at least annually. (See Chapter 14, Section E for when review should occur more frequently and Section F for how the continuing review date is determined.) All of the records listed at §____.115(a)(1)-(4) and 21 CFR 56.115(a) (1)-(4) must be maintained. The clock date starts on the convened meeting date when the study was reviewed. This is the approval date, and IRB approval expires one year from this date. Written progress reports should be received from the clinical investigator for all approved studies prior to the expiration of IRB approval. These reports should include:

written progress reports by PI

- summaries of changes in or deviations from the protocol, including consent form amendments, and
- other supporting documents such as solicitation materials, reports of serious or unexpected adverse events,

and changes to the status of the principal investigator (PI) or subinvestigators, information about the status of subject enrollment and withdrawal, and reports of any additional monitoring group (e.g., DSMB).

Various institutions, sponsors, and/or agencies may have additional requirements related to the content of such progress reports. Copies should be kept of submitted monitoring or site visit reports, as applicable.

The IRB records for each study's initial and continuing review should note when the next continuing review will occur in months or according to other conditions, such as after a particular number of subjects are enrolled. Regardless of the conditions used, the continuing review must not occur more than one year after the last review.

If subjects were never enrolled in a study, the PI's progress report would be brief. Such studies may receive continuing IRB review using expedited procedures. If the study is finally canceled without subject enrollment, records still must be maintained for at least three years after cancellation.

If local investigators are participating in a multicenter research project, they usually are unable to prepare a meaningful summary of project-wide information for their local IRBs. In such circumstances, OHRP guidance recommends that at the time of continuing review, local investigators submit to their local IRBs the most current report from a monitoring entity, if available (e.g., the research sponsor, DSMB). OHRP also encourages institutions engaged in multicenter research projects to use cooperative IRB arrangements for both initial and continuing review.

An IRB could decide to review all studies every quarter. If every quarterly report contains sufficient information for an adequate continuing review and is reviewed by the IRB under procedures that meet FDA requirements for continuing review, FDA would not require an additional annual review.

Documentation of Exemptions

Investigators may submit a request in writing to the IRB to seek exempt status for a research protocol (see Chapter 10 for a more extensive discussion on exemptions). The IRB or its designee (e.g., administrator, chairperson) can review such a request, verify the basis for the exemption, determine whether to approve it, and communicate the determination in writing to the PI. Approval or disapproval should be documented and noted in the file. It is good practice for an institution to require that a knowledgeable person other than the investigator provide the determination of exemption.

Documentation of Expedited Reviews²

Expedited IRB review procedures may be employed only for:

- minor changes in previously approved research during the specified approval period; or
- initial or continuing review of research falling within specific categories published in the Federal Register

Expedited reviews are conducted by the IRB chairperson or a qualified IRB member designated by the chairperson.

Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test Article

FDA regulations at 21 CFR 56.104(c) permit the emergency use of a test article without IRB review. Emergency use is defined as the use of a test article on a human subject in a life-threatening situation for which no standard acceptable treatment is available and for which there is insufficient time to obtain IRB approval (21 CFR 56.102(d)). Written documentation of the emergency use must be submitted to the IRB within five working days of the use. Any subsequent use of the test article requires IRB review. The IRB administrator/manager is responsible for maintaining this documentation in the IRB records. Such an exemption is generally not permitted under DHHS regulations or the Common Rule.

Documentation of Review by Another Entity's IRB

When one or more of an institution's IRB of record is operated by another entity under a separate assurance, the IRB administrator should ensure that accurate records are maintained to document the current IRB approval status of all current and past research. Such records must be easily accessible at all times to personnel and others who have legitimate access rights. If a cooperative review agreement exists, the conditions of that review agreement should be maintained in the file.

An IRB is considered the "IRB of record" when it assumes IRB responsibilities for another institution and is designated to do so through an approved Assurance with OHRP. Typically, a Memorandum of Understanding or IRB Authorization Agreement (IAA) is required designating the relationship for one institution to serve as the IRB of Record for another. An IRB may also choose to enter into an "authorization agreement" with an institution holding a Federalwide Assurance to rely on that institution's review. A "cooperative review agreement" is an agreement reached between two institutions to delineate the responsibilities of each institution with regard to IRB activities.

² See §____.16.110(b); Federal Register 60364-60367 and 60353-60356, November 9, 1998.

Copies of All Correspondence and Communications

It would be difficult to describe all of the possible ways that an IRB could interact with other groups/entities within its institution/organization; however, the IRB's pivotal role in an HRPP increases the likelihood of a large volume of IRB correspondence. These communications might include the IRB's decision on the initial submission, renewals and revisions, notifications of final approval, disapprovals, any appeals filed by the investigator with the IRB, and any communications pertaining to noncompliance. The IRB administrator/manager also must ensure that accurate records are maintained of all correspondence to or from the IRB from investigators, research subjects, cooperating IRBs, and state and federal agencies.

In keeping with the IRB's pivotal role, some of the records and documentation it is required to keep may relate to determinations made by other committees. For example, a clinical protocol that uses radiation may require review by an institutional radiation safety committee before submission to the IRB. The IRB will need to keep materials that document that such a review occurred. In addition, the IRB will have to coordinate activities with the radiation safety committee to make sure the proper reviews are conducted. At the very least, most IRBs will need to maintain communication with investigators and their staff, the official in charge of meeting the obligations under the federal assurance, and outside regulatory agencies such as OHRP or FDA. Depending on how the institutional/organizational HRPP is organized, the IRB may need to maintain close communication with other HRPP components. For example, many IRBs have a procedure for notifying the pharmacy when a protocol that involves an investigational drug has been approved so that the pharmacy knows that a drug can be released when it is requested.

Documentation of the Current Assurance

The IRB files should contain a copy of the current written assurance that the IRB will comply with the requirements of the Common Rule as accepted by the relevant federal office, department, or agency head.

Serious Adverse Event Reports

Assessing adverse events may be challenging for IRBs and investigators because of their ambiguous nature and the complexity of the pertinent regulatory requirements. Investigators have reported frustration in attempting to understand what constitutes an adverse event, the required reporting times, and to whom adverse events should be reported (NBAC 2001).

FDA has specific requirements for reporting adverse events, but they apply to investigators and sponsors rather than IRBs. IRBs should be cognizant of the adverse event reporting requirements of individual protocols (e.g., FDA requirements, NIH requirements, gene transfer requirements) and document all adverse event reports delivered to the IRB, whether required or not. The IRB's SOPs should be clear regarding the IRB's responsibility to analyze and evaluate adverse event reports and should describe the required communication and coordination channels for these reports among other IRBs and safety monitoring entities, such as DSMBs, investigators, sponsors, and federal agencies.

Education and Training Records

Many institutions require written plans for continuing education in human subjects protections for research investigators, IRB members, and IRB staff (see also Chapter 4). In addition, the terms of an assurance generally require continuing education for IRB members (see Chapter 5). The IRB administrator/manager should ensure that accurate records are maintained that list research investigators, IRB members, and IRB staff who have fulfilled the facility's human subjects protection initial and continuing training requirements.

F. Record Retention and Access

In accordance with §____.16.115(b) and 21 CFR 56.115(b), IRB records should be retained for at least three years after the completion of the research with which they are associated. State laws, agency or site-specific policy may supersede this requirement. The IRB's SOP should specify the retention time agreed on by the IRB. All records should be accessible for inspection and copying by authorized representative of sponsoring federal department or agency at reasonable manner.

IRB records should be retained for at least three years after the completion of the research

All material received and retained by the IRB should be considered confidential. Thus, all IRB records should be kept secure in locked filing cabinets or locked storage rooms. Ordinarily, access to IRB records is limited to specified individuals—for example, the IRB chairperson, IRB members, the IRB administrator/manager, IRB staff, and officials of federal and state regulatory agencies, including OHRP and FDA, as applicable. FDA field investigators interview institutional officials and examine IRB records to determine compliance with FDA regulations.³

³ See also the information sheet entitled FDA Institutional Review Board Inspections, available at www.fda.gov/oc/ohrt/irbs/operations.html#board, for a complete description of the inspection process.

Research investigators should be provided reasonable access to files related to their research. All other access to IRB records should be limited to those with legitimate need for them, and the IRB administrator/manager might consider asking consultants and visitors to sign a confidentiality agreement. If applicable, appropriate accreditation bodies could be provided access and may recommend additional procedures for maintaining the security of IRB records.

G. Protocol Tracking

Keeping track of the status of protocols is an essential component of accountability and ensures that appropriate actions are taken by the IRB at appropriate times. This is particularly true for high-volume institutions. The IRB office should maintain a separate file for each research protocol that it receives for review. Each file might contain the following materials, as relevant:

- an IRB research (protocol) application form
- the IRB-approved informed consent document, with the approval date and dates of each change noted on the affected page
- scientific evaluations of the proposed research, if any; for drugs, the Investigator's Brochure; for devices, a report of prior investigations
- applications for federal support (e.g. grants, contracts), if any
- a complete copy of the protocol, research plan, or investigational plan
- advertising or recruiting materials, if any
- applications for protocol amendments or modifications
- continuing review progress reports and related information
- reports of unanticipated problems that involve risks to subjects or others

- reports of adverse events occurring within the agency at reasonable times and in a reasonable manner.
- DSMB reports, if any
- results of any internal quality control and monitoring activities
- results of any external monitoring activities, including reviews provided to the investigator by sponsors, cooperative groups, or federal agencies
- all IRB correspondence to or from research investigators
- all other IRB correspondence related to the research
- documentation of all IRB review and approval actions, including initial and continuing convened (full) IRB review
- documentation of type of IRB review
- documentation of project closeout, including IRB-approved plan for storage/disposition of project data following completion of the research

The IRB administrator/manager should ensure the maintenance of a reliable, computerized research (protocol) tracking system. For most IRBs, a computerized system will be necessary. Such a system should, at a minimum, include the following data fields:

- title of the research (protocol)
- names of PI and co-investigators where appropriate
- funding source (if any)
- date of initial approval
- date of most recent continuing approval
- end of current approval period
- type of review (expedited, convened review or exempt)
- current status (under review, approved, suspended, closed)
- patient or subject complaints

Key Concepts

Administration of IRBs

- The Common Rule and FDA regulations require that institutions and/or IRBs have and implement written policies and procedures to govern the operations and direct the activities of the responsible IRB. Typically, documented IRB SOPs satisfy this requirement when these procedures are implemented by the institution.
- The Common Rule requires that research institutions provide IRBs with sufficient meeting space and staff to support IRB review and record keeping responsibilities. Because of the importance and centrality of an institutional IRB, it may require more resources and administrative support than other institutional committees.
- The duties of the IRB administrator/manager may vary from institution to institution, but they should be defined in an appropriate position description or scope of duties document.
- The Common Rule requires that institutions or the IRB, when appropriate, prepare and maintain adequate documentation of IRB activities.
- Generally, IRB records should include written SOPs; IRB membership rosters; IRB research application files; IRB minutes; documentation of exemptions, expedited reviews, and review by another institution's IRB; IRB correspondence; and cooperative review agreements, assurances, serious adverse event reports, and training records.
- In accordance with the Common Rule, IRB records should be retained by the facility for at least three years after the completion of the research with which they are associated.
- All material received and retained by the IRB should be considered confidential.
- Keeping track of the status of protocols is an essential component of accountability that ensures that appropriate actions are taken by the IRB at appropriate times. This is particularly true for high-volume institutions. The IRB office should maintain a separate file for each research protocol that it receives for review.

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Chapter 10

Types of Institutional Review Board Review

- A. Introduction
- B. Research That Is Exempt from the Common Rule
- C. Research That Is Exempt from Food and Drug Administration Requirements for Institutional Review Board Review
- D. Review of Research by the Convened Institutional Review Board
- E. Expedited Institutional Review Board Review

Key Concepts

References



A. Introduction

In the United States, independent review of proposed research to determine whether it is ethically acceptable is typically performed by local Institutional Review Boards (IRBs) and is one of the primary means by which the current system provides protection to research subjects. Two types of IRB review are described in the federal regulations: full and expedited. Furthermore, some research is exempt from IRB review altogether.

The type and level of review should be responsive to the nature of risk and commensurate with the level of risk involved. For example, the risks and potential benefits arising

type and level of review commensurate with level of risk

in a clinical trial are generally different from those that arise in a study that uses existing data.

Potential harms might vary from physical (e.g., injury or illness) to psychological (e.g., shame or

depression), social (e.g., stigma or discrimination), or legal (e.g., violation of privacy). Within each of these spheres, the probability of harm may range from low to high. The type of review used (e.g., full or expedited) should be matched to the ethical issues and the risks and potential benefits that emerge from the proposed research. For example, all human subjects research involving more than minimal risk

must be reviewed by the IRB at a convened meeting that satisfies certain quorum requirements (§____.108(b); 21 CFR 56.108(c)). For research supported or conducted by the Department of Health and Human Services (DHHS), certain categories of research that are on the expedited review list¹ and that involve no more than minimal risk may be exempt from IRB review or may be reviewed by the IRB through an expedited procedure.

The Common Rule at §____.102(i) and 21 CFR 56.102(i) defines minimal risk as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

For a significant portion of human subjects research, full IRB review is necessary. There is also a substantial subset of human subjects research that may be *exempt* from the general IRB review requirements or eligible for *expedited review*. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one of the more experienced reviewers designated by the chairperson from among the members of the IRB. The reviewers may exercise all of the authorities of the IRB, except the reviewers may not disapprove the research (§____.110(b); 21 CFR 56.110(b)).

¹ See www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm.

The Common Rule provides information and mechanisms for addressing each type of human subjects research subject to the Common Rule. In putting the regulations into practice, the IRB chairperson, usually with the assistance of an IRB administrator, relies on a system of triage to ascertain the level of attention required by any given protocol or protocol modification.

This chapter summarizes the types of review that can be undertaken by an IRB, including the determination that proposed research is exempt from the requirement for review, the criteria for full review or expedited review of research, and the use of subcommittees and other bodies to conduct IRB work or assist in its review.

B. Research That Is Exempt from the Common Rule

There is no exempt IRB review procedure under the regulations. However, some human subjects research conducted or supported by the federal departments or agencies that have adopted the Common Rule is exempt from the regulatory requirements, including those related to IRB review (§____.101(b)). Determinations of exemption must be based on regulatory criteria and should be documented.

Specifically, the regulations at §____.101(b) state that unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from the Common Rule:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special education instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. *(Example: A researcher wants to study a strategy in which second grade teachers read a story twice to students to see if it enhances student recall of key story elements.)*
2. Research that involves the use of educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observation of public behavior, unless information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. *(Example: A researcher conducts an anonymous survey of adult college students to assess trends in eating habits and exercise in the study population.)*
3. Research that involves the use of educational tests (cognitive, diagnostic, aptitude, or achievement), survey procedures, interview procedures, or observations of public behavior that are not exempt under 2, above, if the human subjects are elected or appointed public officials or candidates for public office or federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. *(Example: A researcher wants to study factors that affect policy decisionmaking in elected federal officials by conducting a survey of members of Congress.)*
4. Research that involves the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. *(Example: A researcher wants to examine de-identified medical records to determine if there is a seasonal pattern to emergency room use.)*
5. Research and demonstration projects that are conducted by or subject to the approval of department or agency heads and that are designed to study, evaluate, or otherwise examine public benefit or service programs, procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. *(Example: Researchers in the Department of Veterans Affairs gather data from beneficiaries in assisted living facilities to determine changes in level of services and benefits provided to such beneficiaries.)*
6. Taste and food quality evaluation and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration, Environmental Protection Agency, or Food Safety and Inspection Service of the U.S. Department of Agriculture. *(Example: Researchers developing strategies to improve children's nutritional status ask children to eat two types of cookies with differing nutritional values to determine which type would more likely be consumed.)*

Institutions should clearly identify who will make the determination whether research is exempt from IRB review. Institutions should fully utilize the exemptions whenever appropriate. However, institutions cannot be exempt from the requirements of the Common Rule research that involves activities that go beyond the above categories. Institutions

may require as a matter of policy that research qualifying for exemption under the regulations be reviewed by the IRB if such review is deemed to be in the best interest of the institution. Thus, as in many areas of the federal regulations, the rules regarding exemptions set a “floor” in terms of institutional responsibility, not a “ceiling.” Separate but closely related to the above-mentioned policy, an investigator should not make an exemption determination regarding his/her own research; rather, the investigator should forward a request for the exemption to the IRB or an appropriate institutional official. Although not required by regulation, it is good practice for the IRB administrator (or equivalent) and/or IRB chairperson (or designee) to be responsible for making and documenting each exemption determination.

C. Research That Is Exempt from FDA Requirements for IRB Review

The following categories of clinical investigations are exempt from the Food and Drug Administration (FDA) requirements for IRB review:

- any investigation that commenced before July 27, 1981, and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review by an IRB that meets the FDA requirements in effect before July 27, 1981
- any investigation that commenced before July 27, 1981, and was not otherwise subject to requirements for IRB review under FDA regulations before that date
- emergency use of a test article, provided that such emergency use is reported to the IRB within five working days (subsequent use of the test article at the institution is subject to IRB review (see Chapter 16)); and
- taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture (21 CFR 56.104)

D. Review of Research by the Convened IRB

Research protocols that are not exempt from the Common Rule are vetted by the IRB administrator and/or chairperson to determine the type of review required. If the

proposed research is not eligible for expedited review (see discussion later), then the proposal should be reviewed by the IRB at a convened meeting.

One of the key determinations that must be made by the IRB staff in consultation with the IRB chairperson is the level of risk of the proposed research, because research that involves greater than minimal risk must be reviewed by the convened IRB, while much research that involves no more than minimal risk may be reviewed by the expedited review procedure. When there is doubt about the level of risk involved or if there is doubt about whether the research would receive an adequate review through an expedited review procedure, the IRB staff and chairperson should forward the proposed research to the convened IRB for review.

level of risk of the proposed research

Establishing a Quorum

In order for research to be reviewed and acted upon by the convened IRB, a duly constituted quorum must be present. Under §____.108(b) a quorum must include the following:

- A majority of the members (more than half) must be present
- At least one member whose primary concerns are in nonscientific areas must be present. In addition, the members present at the convened IRB must have appropriate background and expertise sufficient to conduct an adequate review and make all determinations required under §____.111. For example, when biomedical research, including FDA-regulated clinical investigations, is reviewed by the IRB, one or more physician members with appropriate training and credentials should be present for the IRB review
- An alternate member may attend in the place of an absent regular member in order to meet the quorum requirement. Although special consultants can be used to assist the IRB in its review of research, such consultants are not IRB members, cannot be used to establish a quorum, and cannot vote (§____.107(f))
- Should a member be unable to be physically present but be available by phone during a convened meeting, the meeting can be convened via teleconference, as long as all IRB members receive appropriate materials in advance of the meeting and can hear and be heard by each of the other members participating in the convened meeting. Members attending by teleconference are eligible to vote

Use of Primary and Secondary Reviewers

Some IRBs use a system of primary and secondary reviewers in which each regular member of an IRB may be expected to act as a primary reviewer for assigned studies at convened meetings. The primary reviewer usually presents his/her findings based on a review of the application materials and provides an assessment of the soundness and safety of the protocol, recommending specific actions to the IRB. The primary reviewer could also lead the discussion of the study in question. The primary reviewer may be required to review additional material requested by the IRB for the purpose of the study. The secondary reviewer, if assigned, adds to the discussion as necessary. Members of the full IRB vote on the recommendations made by the primary reviewer according to the criteria for approval (see Chapter 11). (Chapters 9 and 11 describe the record keeping requirements of the IRB as well as the IRB review and approval process.)

Use of Subcommittees and Other Specialized Bodies to Support IRB Activities

Research that involves difficult ethical considerations, such as highly innovative interventions or technologies, can be addressed by the IRB in a number of ways. In addition to bringing in nonvoting consultants (as described in Chapter 7), IRBs can establish subcommittees to become particularly well versed or familiar with technical or ethical aspects of an area or category of research. In situations where a particularly challenging or unique protocol is under review, an IRB can request additional review by a body with specific expertise and experience in these special areas.

IRB subcommittees

Some groups, such as the National Bioethics Advisory Commission (NBAC), have suggested that several options should be available for providing an elevated level of specialized review, including specially trained and accredited local IRBs or specially created regional or national review bodies (NBAC 2001). For example, NBAC previously recommended the use of a special standing panel to review research studies that involve persons with mental disorders that may affect their decisionmaking capacity and a national-level review for certain types of stem cell research (NBAC 1999; NBAC 1998).

Some special review bodies already exist at the national level for specific areas of research—for example, the Recombinant DNA Advisory Committee reviews gene therapy protocols (including the consent forms used) at the national level, and Subpart D of 45 CFR 46 provides a mechanism for

the secretary of DHHS, to convene special panels to review certain types of research with children (45 CFR 46.407(b)). A similar provision is available to the FDA commissioner under Subpart D of 21 CFR 50.54. These areas of research are subject to special oversight requirements as a matter of public policy. However, institutions can create additional review bodies to supplement IRB review on an as-needed basis, although there is no requirement to do so except in the two examples provided.

Whether subcommittees are convened to review specific protocols or research is also reviewed by an additional specialized body, the IRB of record at an institution remains the primary and authoritative voting body responsible for reviewing and acting upon research in accordance with the Common Rule and, when appropriate, FDA regulations. When there is an apparent conflict, however, the most stringent standard should apply, whether required by the special review body or the IRB of record.

E. Expedited IRB Review

The Secretary of DHHS has established and has published as a Notice in the *Federal Register*² a list of categories of research that may be reviewed through an expedited review procedure. The list is amended as appropriate after consultation with other departments and agencies and is periodically republished by the Secretary in the *Federal Register*. (Readers are encouraged to consult the most recent version of the list, which changes over time.)³

The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion merely means that the activity is eligible for review through the expedited review procedure when

categories of research that may be reviewed through an expedited review procedure

the specific circumstances of the proposed research involve no more than minimal risk to human subjects. The categories in this list apply regardless of the age of the subjects, except as noted.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; be damaging to the subjects' financial standing, employability, insurability, or reputation; or be stigmatizing, unless reasonable and appropriate protections will be implemented so that the risks related to the invasion of privacy and breach of confidentiality are no greater than minimal. In addition, the expedited review procedure may not be used for classified research that involves human subjects.

² See www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm.

³ See www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm.

Thus, under the current regulatory framework, opportunities exist for streamlining the review process for protocols that are not exempt from review. Research activities that 1) present no more than minimal risk to human subjects and 2) involve only procedures listed in certain categories may be reviewed by the IRB through the expedited review procedure (authorized at §____.110). This review process does not require review by the IRB at a convened meeting.

Expedited review procedures are described at §____.110. Under an expedited review procedure, the IRB chairperson, or one or more experienced reviewers designated by the chairperson from among the members of the IRB, reviews the research protocol. The IRB is required to adopt a method for keeping all IRB members advised of research proposals that have been approved under the expedited review procedure. In conducting expedited review, the IRB reviewers may exercise all of the authorities of the IRB, except they may not disapprove the research. A research activity may be disapproved only after review by the convened IRB in accordance with the nonexpedited procedure set forth at §____.108(b). Under §____.110(d), the department or agency may restrict an institution's or IRB's authority to use the expedited review procedure.

Like review by the convened IRB, expedited review must fulfill all the requirements of review found at §____.111 and, if applicable, at 45 CFR 46 Subparts B, C, and D, and 21 CFR 50, Subparts A, B, and D, and Part 56. IRBs are reminded that the requirements for informed consent (or for altering or waiving the requirement for informed consent) apply regardless of whether research is reviewed by the convened IRB or under an expedited procedure.

The Office for Human Research Protections (OHRP) provides that any institution with an OHRP-approved assurance may use expedited review for initial or continuing review of federally funded or conducted research and for the review of minor changes in previously approved research as described at §____.111(b)(2).

Consultants may assist the IRB in the review of issues that require expertise beyond or in addition to that available on the IRB. Only the IRB chairperson, or one or more experienced reviewers designated by the chairperson from among members of the IRB, may carry out the expedited review. The person conducting the expedited review may give approval, require modifications (to secure approval), or refer the research to the convened IRB for review in accordance with the nonexpedited review procedures set forth at §____.108(b).

Finally, OHRP guidance recommends that:

- documentation for initial and continuing reviews conducted under an expedited review procedure include:
 - the specific permissible categories justifying the expedited review and
 - documentation of the review and action taken by the IRB chairperson or designated reviewer and any findings required under the regulations
- written IRB procedures include a description of policies describing the types of minor changes in previously approved research that can be approved under an expedited review procedure in accordance with the regulations at §____.110(b)(2) and
- expedited review procedures NOT be used for research involving prisoners. However, if an IRB chooses to use expedited review for research that involves prisoners, OHRP recommends that the prisoner representative of the IRB be one of the designated reviewers.⁴

The IRB chairperson (or designated reviewer) can exercise all of the authorities of the IRB, except that he/she may not disapprove the research. A research proposal may be disapproved only after review by the convened IRB. When the expedited review procedure is used, all regular members of the IRB must be informed at the next convened meeting, of the actions taken (§____.110(c)).

IRBs are reminded that all determinations required for IRB approval (see §____.111) still must be made and the requirements for obtaining and documenting informed consent (or waiver, alteration, or exception of these requirements) apply regardless of the type of review—expedited or convened—employed by the IRB.

Research Categories That Qualify for Expedited Review⁵

Once it is determined that the research can be classified as minimal risk, then, to qualify for expedited review, it must meet at least one of the following categories:

1. Clinical studies of drugs and medical devices only when condition a or b (below) is met:
 - a. research on drugs for which an Investigational New Drug application (IND) (21 CFR Part 312) is not required⁶ or
 - b. research on medical devices for which
 - i) an Investigational Device Exemption (IDE) application (21 CFR Part 812) is not required or
 - ii) the medical device is cleared/approved for marketing, and the medical device is being used

⁴ Guidance, dated August 11, 2003, is available at www.hhs.gov/ohrp/humansubjects/guidance/exprev.htm.

⁵ See www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm.

⁶ Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

- in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - a. from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL within an eight-week period, and collection may not occur more frequently than two times per week; or
 - b. from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kg in an eight-week period, and collection may not occur more frequently than two times per week.
 3. Prospective collection of biological specimens for research purposes by noninvasive means.⁷
 4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.⁸ Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
 5. Research that involves materials (data, documents, records, or specimens) that have been collected or that will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).⁹
 6. Collection of data from voice, video, digital, or image recordings made for research purposes.
 7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.¹⁰
 8. Continuing review of research previously approved by the convened IRB as follows:
 - a. where
 - i) the research is permanently closed to the enrollment of new subjects
 - ii) all subjects have completed all research-related interventions
 - iii) the research remains active only for long-term follow-up of subjects; or
 - b. where no subjects have been enrolled and no additional risks have been identified;¹¹ or
 - c. where the remaining research activities are limited to data analysis.
 9. Continuing review of research, not conducted under an IND or IDE where categories 2 through 8 do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified (OPRR 1998).

⁷ Examples: hair and nail clippings in a nondisfiguring manner; deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; permanent teeth if routine patient care indicates a need for extraction; excreta and external secretions (including sweat); uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; placenta removed at delivery; amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; and sputum collected after saline mist nebulization.

⁸ Examples: physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; weighing or testing sensory acuity; magnetic resonance imaging; electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; and moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

⁹ Some research in this category may be exempt from the Department of Health and Human Services (DHHS) regulations for the protection of human subjects at 45 CFR 46. This listing refers only to research that is not exempt.

¹⁰ Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.

¹¹ Of welcome news to institutions, the Office for Human Research Protections has interpreted this to mean that, in the context of multisite research, expedited review may be conducted for continuing review at a site where no subjects have been enrolled, even if subjects have been enrolled elsewhere.

Key Concepts: Types of IRB Review

- The type and level of IRB review should be responsive to the nature of risk and commensurate with the level of risk involved.
- Some human subjects research conducted or supported by the federal departments or agencies that have adopted the Common Rule may be exempt from the regulations requiring IRB review (§____.101(b)). Determinations of exemption must be based on regulatory criteria and should be documented. These determinations should be made by the IRB or an appropriate institutional official, not by the investigator.
- It is the investigator's responsibility to claim the exemption to the IRB so that it is verified and documented.
- The IRB administrator (or equivalent) and/or IRB chairperson (or designee) are responsible for evaluating and documenting submissions that claim exemption from IRB review.
- Except when an exemption has been documented, research protocols are vetted by the IRB staff in consultation with the IRB chairperson to determine the type of review to be assigned. If the proposed research is determined to be greater than minimal risk or is otherwise not eligible for an expedited review procedure, the proposal must be reviewed by the IRB at a convened meeting at which a quorum is present.
- IRBs can establish subcommittees to become particularly well versed or familiar with technical or ethical aspects of an area or category of research; however, the full committee must discuss and vote on the proposals.
- For research that is not exempt from the requirements of the Common Rule, opportunities nonetheless exist for streamlining the review process. Research activities that present no more than minimal risk to human subjects and involve only procedures listed in certain categories may be reviewed by the IRB through the expedited review procedure.
- The Secretary of DHHS has established a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list is amended, as appropriate after consultation with other departments and agencies. Readers are encouraged to consult the most recent version of the list, as it changes over time.
- IRBs are reminded that all determinations required for IRB approval (see §____.111; 21 CFR 56.111) still must be made, and the requirements for obtaining and documenting informed consent (or waiver, alteration, or exception of these requirements) apply regardless of the type of review—expedited or convened—employed by the IRB.
- Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB, except that the reviewers may not disapprove the research.

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Chapter 11

Institutional Review Board Review and Approval

- A. Introduction
 - B. Regulatory Requirements
 - C. Scientific Review
 - D. Assessing Risks and Potential Benefits
 - E. Institutional Review Board Review of the Recruitment and Selection of Research Subjects
 - F. Institutional Review Board Review of the Informed Consent Process and Document
 - G. Institutional Review Board Review of the Need for a Data Safety Monitoring Plan
 - H. Frequency of Review
 - I. Compliance with All Applicable State Laws
- Key Concepts**
References



A. Introduction

Current regulatory requirements place central responsibility for protecting human subjects of research with the Institutional Review Board (IRB). The purview of any given IRB can be quite broad, encompassing a wide array of research conducted by many individuals and/or institutions. For every protocol that is subject to the regulations—that is, protocols involving the study of identifiable living persons or information about them in order to produce generalizable knowledge or clinical investigations regulated by the Food and Drug Administration (FDA)—the IRB must make a series of determinations to ascertain the type of review needed and the acceptability of the proposed study.

The principles outlined in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (Belmont Report)* provide the foundation for IRB review (National Commission 1979). For example, the application of the ethical principle of respect for persons gives rise to the concern for a subject's vulnerability and autonomy; the application of the principle of beneficence leads to the necessity of assessing risks and potential benefits; and the principle of justice requires investigators to be fair and cautious in recruiting research subjects, particularly in relation to the inclusion of individuals categorized as vulnerable. In addition to these general ethical principles, the Common Rule and FDA regulations provide a regulatory

framework for proceeding with the review. The assessment of a research protocol in light of these principles and requirements often requires careful consideration of a substantial array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, IRB review presents both an opportunity and a responsibility to gather systematic and comprehensive information about the proposed research protocol.

Many criteria must be met for an IRB to do its job well. Previous chapters in this resource manual address issues concerning IRB education (Chapter 4), IRB membership (Chapter 7), IRB roles and authorities (Chapter 8), and administration of the IRB (Chapter 9). This chapter focuses on the types of IRB review that can occur and the substance of the IRB review process itself—that is, what the IRB should consider when a research protocol is submitted for its deliberation—including the science involved, the risks and potential benefits, the recruitment and selection of subjects, the informed consent process, the need for monitoring once the study has begun, the frequency of review, and compliance with other regulatory or legal requirements.

B. Regulatory Requirements

The regulatory requirements for IRB approval of research are the minimal starting points for the substantive aspects of

review. FDA regulations at 21 CFR 56.111 and the Common Rule at §____.111 provide the following framework for approval of research.

In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

1. Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk and, whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to be gained. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research that involves vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by §____.116 or 21 CFR 50.20 and 27.
5. Informed consent will be appropriately documented in accordance with and to the extent required by §____.117 and 21 CFR 50.27 and 56.109(c)(1).
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have

been included in the study to protect the rights and welfare of these subjects.

The principle of beneficence states that persons should be “treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being” (National Commission 1979, 6). Therefore, this principle, which provides a focal point for review, requires that investigators attempt to maximize possible benefits and minimize possible harms. In research, however, the process of gathering data to gain knowledge of benefit to society may expose some individuals to harm, and IRBs must determine, therefore, “when it is [ethically] justifiable to seek certain benefits despite the risks involved, and when the [potential] benefits should be foregone because of the risks” (National Commission 1979, 7). Such an analysis of risks and potential benefits often will be complex, because IRBs are called on to assess the balance between any number and type of risks and potential benefits.

maximize possible benefits and minimize possible harms

A first critical step, however, is determining whether the proposed scientific basis and research design are sound. If the research question being asked cannot be answered by the proposed study, then it is wrong to engage human volunteers in such an effort.

C. Scientific Review

If a research study is so methodologically flawed that little or no reliable information will result from it, it is unethical to put subjects at risk or even to inconvenience them through participation in such a study. The Common Rule does not clearly call for IRB review of the scientific validity of the research design. Nonetheless, it does require that IRBs determine whether “[r]isks to subjects are reasonable in relation to... the importance of the knowledge that may reasonably be expected to result” (§____.111(a)(2); 21 CFR 56.111(a)(2)). Thus, it is critical that the IRB determine that the research question is valid, the methodology will answer the question, and the research design will minimize harms while maximizing benefits (Weinberg and Kleinman 2003). More specifically, it is important to consider whether the research outcomes are clearly defined potential sources of bias have been identified and addressed, control groups are appropriately defined and their risks assessed, appropriate methods of randomization are to be used and justified, and sample size is sufficient and justified (Weinberg and Kleinman 2003). Moreover, the design of clinical trials should be based on sound statistical principles and methodologies, with clear study termination rules.

Thus, the human research protection program (HRPP) or the entity conducting or sponsoring the research should ensure that all protocols submitted to an IRB undergo an independent and rigorous scientific review to assess scientific quality, the importance of the research to increase knowledge, and the appropriateness of the study methodology to answer a precisely articulated scientific and, in some cases, clinical question. Ensuring that the chosen study design minimizes bias and generates data that will answer the scientific question requires some understanding of the research process and the area under study. These issues are pivotal to a successful study, and many believe they should be evaluated by a mechanism that is distinct from the ethical review process before subjects are enrolled (IOM 2003).

rigorous scientific review to assess scientific quality

The ability of an IRB to conduct a rigorous scientific review of a protocol will vary by IRB and by institution. There may be situations in which adequate scientific expertise is assembled within one IRB. As discussed in Chapters 7 and 8, IRBs can call on consultants and external reviewers to assist with the review of the scientific and technical aspects of a study. However, some have suggested that the IRB should not be the only review body assessing the scientific merit of a proposal (IOM 2003). When an IRB is called on to conduct the exclusive scientific review of a protocol, two primary problems can arise:

- it can be distracted from intensive review of the ethical issues due to lack of time
- it may lack the scientific expertise necessary to adequately assess the technical merit of a proposal (DHHS OIG 1998).

A variety of mechanisms can be used to ensure independent scientific review. In fact, most protocols currently undergo some level of scientific review through existing mechanisms—for example, scientific review committees in industry, study sections or peer review committees at federal agencies that sponsor research, and academic department review of institutionally funded research.

If protocols involve investigational drugs, devices, or biologics, they must be submitted to FDA for regulatory review, after which they could be rejected by the agency on scientific or safety grounds. FDA reviewers are also trained scientists and physicians with expertise in the relevant therapeutic area and familiar with issues of, for example, inclusion/exclusion, appropriate endpoints, and safety issues. Comments provided to sponsors by FDA reviewers should be made available to the IRB to inform the final comprehensive assessment of a protocol.

There always will be some level of overlap between scientific and ethical reviews, and in many cases the IRB could be sufficiently expert to conduct all aspects of a review, perhaps seeking some external advice as needed. As noted by the Institute of Medicine in its report *Responsible Research: A Systems Approach to Protecting Research Participants* (2003), one advantage of ensuring a distinct scientific review is the opportunity to identify protocols that are not yet suitable for IRB consideration, thereby maximizing IRB time to focus on fully developed, scientifically sound protocols.

D. Assessing Risks and Potential Benefits

An IRB's assessment of risks and benefits is a method for determining whether the anticipated benefits to be gained by conducting the research justify any risks to which the subjects might be exposed. For prospective subjects, this assessment by the IRB will assist their determination of whether or not to participate (National Commission 1979). The requirement that research must be justified on the basis of a favorable risk-benefit assessment bears a close relationship to the principle of beneficence. In the *Belmont Report*, the National Commission for the Protection of Human Subjects wrote:

The term “risk” refers to a possibility that harm may occur. However, when expressions such as “small risk” or “high risk” are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term “benefit” is used in the research context to refer to something of positive value related to health or welfare. Unlike “risk,” “benefit” is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm.

Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits.

It is commonly said that benefits and risks must be “balanced” and shown to be “in a favorable ratio.” The metaphorical character of these terms draws attention to the difficulty of making precise judgments (1979, 4).

The IRB should conduct some fundamental assessments in its determination of risks and potential benefits. First, it must evaluate whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies. Second, it should determine whether it is in fact necessary to use human subjects at all. If the use of human subjects is determined to be essential and the investigator's estimation of risks and potential benefits appears sound, then the IRB must make a series of assessments to gauge the risk-benefit ratio and determine the level of protections needed. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. Risks should be reduced to those necessary to achieve the research objective (National Commission 1979).

a series of assessments to gauge the risk-benefit ratio

The assessment of risks and potential benefits is arguably the most important and challenging responsibility of an IRB. As noted above, §____.111(a) and 21 CFR 56.111(a) require that IRBs determine that risks to subjects are minimized and are reasonable in relation to anticipated benefits. Toward this end, the description, quantification, and analysis of risks and benefits are essential to the performance of both initial review and continuing review of research by IRBs. A central consideration is whether the research poses minimal risk, because the answer to that question sets in motion a series of decisions about the type of review that should take place and whether a waiver of consent can be considered.

Defining Minimal Risk

Current federal regulations for the protection of research participants call for the classification of research as involving either minimal risk or greater than minimal risk. As defined in the federal regulations:

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (§____.102(i); 21 CFR 56.102(i)).

This classification is ethically relevant, because it is intended to provide protection to research subjects by focusing IRB attention on riskier research. When used as a sorting mechanism, this classification determines the level of review required of an IRB. For example, under the current regulations, if a research study is determined to pose only minimal risk and involves a procedure contained on the expedited review list, it may be evaluated by using the

expedited review process in which the IRB chairperson or a designee may review the research study in accordance with all the required regulations (§____.110(b); 21 CFR 56.110(b)) (see Chapter 10 for a discussion of expedited review).

Research involving more than minimal risk requires full IRB review. As the risk of research increases above the minimal risk threshold, protections for subjects should become more stringent. For example, with greater than minimal risk research, the process of informed consent cannot be waived or altered (§____.116(d)). There is no provision for waiver of consent in the FDA regulations, except in the case of emergency research (see Chapter 16).

The definition of minimal risk in federal regulations does not specify an unambiguous standard. That is, risks involved in the proposed research are compared to those encountered in daily life, but it is unclear whether daily life applies to healthy individuals or to the target group of the research (e.g., people with heart disease, children with learning disabilities).

Existing sources of guidance offer conflicting interpretations of the standard to be used in determining the level of risk. In the context of research involving children, the National Commission defined a so-called absolute standard when it defined minimal risk as "the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children" (National Commission 1977). This standard was not adopted in the regulations pertaining to research involving children (45 CFR 46 Subpart D) (see Chapter 21). However, the Department of Health and Human Services (DHHS) regulations concerning research involving prisoners limit minimal risk to the experience of healthy individuals.

In 1993, the Office for Protection from Research Risks (OPRR) endorsed such an absolute standard interpretation for Subpart A of the Common Rule (Ellis 1995). OPRR's interpretation is inconsistent with DHHS' intention as expressed in the preamble of the 1981 version of 45 CFR 46, which is a relative standard: "the risk of harm ordinarily encountered in daily life means those risks encountered in the daily lives of the subjects of the research."

If minimal risk is not characterized in terms of the daily life and experiences of healthy individuals, then it might be taken to refer to the daily life and experiences of the research subject. If this is the case, then the same intervention could be classified as minimal risk or greater than minimal risk, depending on the health status of the research subjects and their particular experiences. A relative standard for minimal risk would allow ill participants to be exposed to greater risks

than healthy participants, which in practice is sometimes the case in research involving the terminally ill.

In general, however, IRBs are likely to use a standard that is related to the risks of daily life that are familiar to the general population for determining whether the level of risk is minimal or more than minimal—for example, driving to work, crossing the street, or flying across the country. Using this standard, research involves no more than minimal risk when it is judged that the level of risk is no greater than that encountered in the daily lives of those in the general population.

When a research study is determined to involve no more than minimal risk, the IRB should also consider whether the procedures in question pose additional risks to some fraction of the potential research subjects. In such cases, additional protections might be required to reduce the level of risk among that subgroup. For example, drawing a small quantity of blood normally would be considered a minimal risk procedure; its risks do not exceed those normally encountered by the general population. However, if a particular research study involved subjects with immunosuppressive or bleeding disorders, drawing blood could pose a higher level of risk, and additional protections might be required.

It must be stressed that, in making the determination that a research study involves no more than minimal risk, the IRB must take into consideration all types of risk posed. For example, a research study involving drawing blood to study one's predisposition to breast cancer might involve not only the relatively inconsequential physical risks associated with drawing blood but also all the psychological risks that might be associated with learning one's status or having that information released to people or institutions other than the investigator and his/her research team.

Minimal Risk and Vulnerable Populations

DHHS regulations on research involving fetuses and pregnant women (45 CFR 46 Subpart B), research involving prisoners (45 CFR 46 Subpart C), and research involving children (45 CFR 46 Subpart D and 21 CFR 50 Subpart D) strictly limit research presenting more than minimal risk. These studies place additional responsibilities on IRBs in their review process (see Chapter 21 for a discussion of research with vulnerable subjects). In addition, the National Commission recommended special limitations on research presenting more than minimal risk to persons institutionalized as mentally disabled. For such subjects, the commission recommended that minimal risk be defined in terms of the risks normally encountered in the daily lives or the routine medical and psychological examination of healthy subjects. IRBs should therefore determine whether the proposed

subject population would be more sensitive or vulnerable to the risks posed by the research as a result of its general condition or disabilities. If so, the procedures would constitute more than minimal risk for those subjects. (Research involving vulnerable populations is discussed in greater detail in Chapters 20 and 21 of this resource manual.)

Types of Risk

In general, risks can be categorized as physical, psychological, or social. Any of these forms of risk may occur in any type of research project, but physical risks are more likely to occur in biomedical studies than in behavioral or social science research. IRBs should recognize that these categories of risk are somewhat changeable, in that a given risk may fall into two or more of the categories or multiple types of risk may be present in a single study.

Physical risks are usually thought of as the possibility of pain, discomfort, or physical injury. Such harms may be easy to identify in certain biomedical studies, but physical risks can be difficult to anticipate in studies first conducted in human populations or when the protocol involves withholding or withdrawing effective therapy.

physical risks

Psychological risks may be readily apparent or difficult to assess in the short term, and they are often less quantifiable than physical risks. For example, research involving genetic testing may have psychological risks associated with the disclosure of a subject's likelihood of developing a chronic disease or the passing of a deleterious trait to a child (see Chapter 24). Behavioral studies may reveal traits about an individual that he/she is uncomfortable discovering or having others discover (see Chapter 17). Administration of a survey on a sensitive topic, such as child or sexual abuse, can provoke feelings of guilt, distress, and anger. In some studies, generating psychological distress is expected and may be an endpoint of the study itself.

psychological risks

Research subjects also can experience social or economic risks—that is, risk of stigmatization or discrimination as a result of research results that classify an individual according to a particular trait (e.g., intravenous drug user, sex worker). Discrimination can be cultural, economic, or occupational. Social risks are particularly associated with studies of private aspects of human behavior, such as sexual preference. The possibility of a breach of confidentiality is often the most significant risk of such research. The degree of risk, however, is related to the sensitivity of the research data from the subject's perspective and the likelihood that unauthorized individuals could gain access to the data. Some invasions of privacy and breaches of confidentiality could result in embarrassment within one's business or

social group, loss of employment, or criminal prosecution. The IRB should focus on whether the investigator has taken precautions to ensure that such “preventable harms” do not occur—that is, that confidentiality safeguards are in place (see also Chapter 13 on privacy issues).

Although most assessments of risks focus on risks of harm to research subjects, risks may also ensue to others not directly involved in the research. For example, there may be legal risk to parents in a study of illegal activity by their minor children, and certain racial/ethnic groups might be placed at risk by research that targets specific characteristics associated with a given minority group.

social or economic risks

Identification and Quantification of Risks

To identify the risks of research, IRBs must ensure that the investigator has presented in the protocol a comprehensive review of the potential harms that may occur. It is incumbent on the IRB to review this information for accuracy and completeness. If the IRB determines that it cannot make such an assessment, it should seek the advice of outside experts. Identifying the risks is important not only in weighing the potential benefits of the research but also in determining whether the consent process and consent form are accurate and complete.

When possible, risks should be quantified and appropriately characterized in the informed consent process. Risk quantification takes into account the likelihood of an occurrence and the potential severity of the harm. Severity, in turn, depends on the type of harm, its duration, its permanency, or the extent to which it may alter or affect a subject’s lifestyle. Quantification of risk (e.g., 10 percent, 1 in 100) helps the IRB accurately assess risk and ensure the adequacy of disclosure in the informed consent document. Quantification of risk may be the best way that a subject can assess the significance of potential risks. In its preamble to the informed consent regulations, FDA emphasizes the desirability of risk quantification, stating that “where such descriptions or disclosures may contain quantified comparative estimates of risk or benefits they should do so.”¹

risk quantification

Identification and quantification of risk also allow the IRB to determine which protocols require continuing review more often than annually, as appropriate to the degree of risk (§____.103(b)(4) and §____.109(e); 21 CFR 56.109(f)). The Office for Human Research Protections (OHRP) recommends that the minutes of IRB meetings clearly reflect these

determinations regarding risk and approval period (review interval).

Minimizing Risk

The Common Rule requires that the IRB must determine that the probability of the occurrence and severity of the risks is minimized by using “procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk” (§____.111(a)(1); 21 CFR 56.111(a)). Although some risks cannot be minimized, the IRB should ensure that the investigator has done everything possible in the research design to reduce risk likelihood and magnitude. For example, the IRB can ensure that the investigator and study personnel are qualified to perform the procedures involved in the research, that the inclusion and exclusion criteria (discussed below) appropriately consider minimization of risk, that study termination rules are clear and unambiguous, and that subjects are properly monitored (also discussed below).

Assessing Potential Benefits

Research is conducted with a wide variety of goals but with the common purpose of producing generalizable knowledge. A critical aspect of IRB review is determining the potential benefits of the proposed research. Typically, research on therapeutic interventions also has the potential to provide a direct medical benefit to the subject. Other types of research, such as Phase 1 drug studies or survey research, are likely to provide little or no direct benefit to the subject, other than a sense of altruism. The principles of justice and respect for persons require that individuals not be deprived of an opportunity to participate in research unless there is a compelling reason to do so. Whenever there is a prospect of direct benefit to the subject, IRBs must be cognizant of the fact that these potential benefits may be so significant that they have the potential of unduly influencing a patient to participate in high-risk research that he/she would not otherwise consider.

In addition to benefits that might accrue to research subjects, IRBs also must consider potential benefits to society at large or to special groups of subjects in society. Societal gain without the prospect of direct benefit to the subject, however, may not be sufficient justification for a study, especially when vulnerable populations are involved.

Risk-Benefit Analysis

The IRB is obligated to ensure that the risks to subjects are reasonable in relation to anticipated benefits. In addition to the Common Rule, several national and international

¹ See www.fda.gov/oc/gcp/preambles/46fr8958.html.

codes governing human subjects research—including the World Medical Assembly’s *Declaration of Helsinki*, the guidelines of the Council for International Organizations for Medical Sciences, and the Medical Research Councils of Canada and the United Kingdom—also require a favorable risk-benefit relationship in research.

This final balancing of identifiable risks and potential benefits is the most difficult task for the IRB, because research is an inherently uncertain endeavor. In some cases, the calculus might be clear; in others it can be more difficult to assess because the risks and potential benefits lack a basis for comparison and might accrue differently to individuals in a given protocol. The IRB is making a prospective judgment. Its greatest contribution is to make that difficult determination and then ensure that the information is communicated to each potential subject so that he/she can make an autonomous choice about participation. The risk-benefit assessment is not a technical one that is valid under all circumstances; rather, it is a judgment that often depends on prevailing community standards and subjective determinations of risk and benefit. Consequently, different IRBs may arrive at different assessments of a particular risk-benefit ratio. The risk-benefit analysis also can become more

**prevailing
community
standards**

difficult when the potential benefits accrue to society rather than directly to the subjects of the research.

E. IRB Review of the Recruitment and Selection of Research Subjects

IRB approval of a protocol also requires that the selection of subjects is equitable. Selection of research subjects addresses the principle of justice, as elaborated in the *Belmont Report*.

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of “fairness in distribution” or ‘what is deserved.’ For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not

unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research (National Commission 1979).

IRBs must know what types of individuals (e.g., healthy individuals, patients, children) the subjects will be, what incentives are being offered, and the conditions under which the offer will be made. Appropriate subject selection—excluding those individuals who would be at greater risks or including those most likely to benefit—can be an important means for minimizing risks. Thus, the IRB should scrutinize the inclusion and exclusion criteria for proposed studies.

**inclusion and
exclusion criteria
research subjects**

According to a 2000 report by the DHHS Office of Inspector General, two-thirds of the IRBs responding to a survey expressed concern about current practices used to recruit human subjects. The IRBs had particular concern about those practices that occurred apart from the actual investigator-subject interaction. Recently, sponsors and contract research organizations have been assisting research sites to recruit by initiating national recruitment campaigns for multisite trials. The national efforts have spawned a new industry of patient recruitment firms and research marketing companies that are creating professional, elaborate marketing packages. Many of these national advertisements include toll-free numbers. Call centers may provide operators who can screen respondents according to the trial’s eligibility criteria and can schedule appointments at sites most convenient to callers or the toll-free number may automatically transfer to a phone at the closest site (DHHS OIG 2000). In addition, investigators and sponsors raised concerns about the increased pressure to recruit subjects in a timely manner.

The concerns that IRBs, sponsors, and investigators have about recruitment practices relate, in various ways, to the implications for informed consent. Misleading information could shape subjects’ initial judgment about a research study and thus influence decisions about participating.

Under federal regulations, the IRB must review and approve the methods used to recruit subjects to ensure that the methods are not coercive and that the confidentiality and privacy of potential subjects are protected (see also Chapter 12 for more extensive discussion regarding recruitment) (§____.111(a)(3); 21 CFR 56.111(a)(3)). Every protocol should include a recruitment section that clearly describes the following:

- how potential subjects are identified
- how and by whom subjects are approached about participation
- when consent is obtained in relation to the start of

- the study procedures; and
- whether third parties (calling centers/centralized screening centers) will assist with the recruitment of subjects

IRB Review of Methods for Identifying Subjects

IRBs should review how subjects will be identified to ensure that their confidentiality is protected and that selection is equitable. Subjects with specific diseases or conditions are often identified as potential subjects through some type of record (e.g., registries, physician or hospital records, employment or school records). Controls can be individuals in the same subpopulation as the subjects (which would be the case in a randomized clinical trial), those with unrelated conditions, or healthy volunteers from the general population. If potential subjects are identified through medical records, log books, physicians' records, or other records that are not public documents, the IRB should make certain that the following conditions have been met: (1) the investigator is allowed access to such records by the institution or the physician and (2) responsibility for confidentiality and protection of privacy is clearly accepted by the investigator (see also Chapter 13 for extensive discussion about the Privacy Rule).

Sometimes it might be necessary for an investigator to review thousands of medical records to identify a very small number of subjects who are suitable for a study. Such "screening" procedures have been a topic of confusion, with uncertainty about the role of the IRB and the need for consent from individuals whose records might be perused.

Procedures that are to be performed as part of the practice of medicine and that would be conducted whether or not study entry was contemplated—such as for the diagnosis or treatment of a disease or medical condition—may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent may need to be obtained prior to the initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research. When a physician-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted (see Chapter 12 for an extensive discussion of the informed consent process).

**screening
procedures for
determining
research
eligibility**

Screening procedures for determining research eligibility are considered part of the subject selection and recruitment process

and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure, the IRB may choose to use expedited review procedures. The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests, including a brief summary description of the study in which they may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

An alternative in some circumstances may be the use of a "data broker," that is, an intermediary who already has access to the data. The broker can review records to identify appropriate subjects whose consent to participate in the study can then be sought. With automated record-keeping systems, it may be easier to identify appropriate subjects without reviewing all the records. Where the records are not computerized, however, IRBs will have to decide under what conditions an investigator may scan thousands of medical or other private records while searching for a small number of appropriate subjects. One factor to consider would be the sensitivity of the information likely to be contained in the records. For example, did the patients have broken ankles or abortions? Were they treated for strep throat or a sexually transmitted disease? Another factor to consider is the type of information the investigator wishes to obtain from those who are selected as suitable subjects for the study.

IRB Review of the Use of Advertising

Advertising to recruit research subjects is not, in itself, an objectionable practice; the posters, flyers, mailings, and newspaper advertisements that may be used for such recruitment are legitimate methods for informing people of studies that they might be interested in joining. When advertising is to be used, however, IRBs should review the information contained in the advertisement, as well as the mode of its communication, to determine whether the procedure for recruiting subjects affords adequate protection. IRBs should review advertising to assure that it is not unduly coercive and that it does not promise a certainty of cure beyond what is outlined in the consent and the protocol. Thus, IRB review is necessary to ensure that advertising information is not misleading to subjects, especially when a study will involve persons with acute or severe physical or mental illness or persons who are economically or educationally disadvantaged. The IRB should review the final copy of printed advertisements to evaluate not only the verbal

content, but the relative size of type used and other visual effects.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection processes. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study.

When advertisements are to be taped for broadcast, the IRB should review the final audio-/videotape. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of the text of the message before taping in order to avoid re-taping because of inappropriate wording.

When advertisements are easily compared with the approved consent documents, the IRB chairperson, or other designated IRB member, may review and approve advertisements by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

Consideration of Remuneration for Participation

Another issue of justice, as well as of respect for persons, involves remuneration² for participation in research. Paying research subjects is “a common and long-standing practice in the United States” (Dickert et al. 2002, 368), perhaps because of the need to provide incentives as part of recruitment and because the moral principles of fairness and gratitude support providing payment to those who bear the burdens of research on behalf of society. In any event, difficult questions remain: How much money should research subjects receive? For what should they receive payment—their time, inconvenience, discomfort, or level of risk? Can remuneration—or some level of remuneration—create a problem for research subjects’ voluntary, informed consent?

Although the consensus is that remuneration for participation in research should be just or fair, there is little agreement in theory or in practice about what constitutes just or fair payment. Furthermore, federal regulations and guidance are relatively silent on this subject, warning about “undue influence” without, however, specifying what counts

as undue. One major ethical concern is that payments should not be so high that they could compromise a prospective subject’s examination and evaluation of the risks or the voluntariness of his/her choices. This concern is greatest, of course, when the studies involve significant risks. However, undue influence depends on context, because, wherever the remuneration is set, it will influence the decisions of some more than others. In particular, it will be more important to those for whom it will make a significant financial difference. Other concerns are that payments should not be so low that they serve to recruit disproportionately high numbers of economically disadvantaged persons and that participants should be fairly paid for their contribution to research.

remuneration for participation in research should be just or fair

Some institutions have adopted policies regarding the recruitment and payment of volunteers. In general, they attempt to minimize the possibility of coercion or undue influence by requesting that subjects be recruited by open, written invitation rather than by personal solicitation. IRBs should try to ensure that the consent document contains a detailed account of the terms of payment, including a description of the conditions under which a subject would receive partial payment or no payment (e.g., what will happen if subjects withdraw part way through the research or if the investigator removes them from the study for medical or noncompliance reasons).

In more complex research projects, IRBs tend to base their assessment on the prevailing payment practices within their institutions or general locales. Volunteers are often compensated for their participation according to an established fee schedule, based on the complexity of the study, type and number of procedures to be performed, time involved, and anticipated discomfort or inconvenience. Standard payments may be established for each tissue or fluid sample collected, depending on the type of sample (blood, urine, or saliva) and the time (day or evening) the sample is to be collected. Alternatively, subjects may be paid an hourly rate or a fixed amount, depending on the duration of the study and whether the study requires admission to a research ward. Extra payments are usually provided for a variety of additional inconveniences (e.g., the imposition of dietary restrictions). Payments may vary according to a number of factors, and, therefore, to judge the appropriateness of payments, IRBs may need to become familiar with the accepted standards within their community as well as the anticipated discomforts and inconveniences involved in a

² The IRB Guidebook (available at www.hhs.gov/ohrp/irb/irb_guidebook.htm) proposes that the term “remuneration” be used for payment for participation in research and that “compensation” be reserved for payment or provision of medical care for research-related injuries.

particular study. Some institutions have placed a ceiling on the amount an individual may earn in any one study or during a given length of time (e.g., per year, per semester).

IRB members tend to approach the problem of assessing the risk from payment from one of two positions. One side argues that normal healthy volunteers are able to exercise free choice and that, because judging the acceptability of risk and weighing the benefits is a personal matter, IRBs should refrain from imposing their own views on potential subjects. According to this view, IRB responsibility should be confined to ensuring that consent is properly informed. Other IRB members might argue that the IRB should protect potential subjects from inducements that may affect their ability to make an informed, voluntary choice. It should be noted that, in this context, incentives need not be financial to cause problems. The provision of free health care for persons with limited resources and major medical problems may be a significant inducement to participate in research (even if the research activity is nontherapeutic). There is no consensus regarding whether this kind of inducement is unacceptable. In assessing this potential problem, IRBs might consider whether only the destitute agree to volunteer or whether those who can obtain good medical care on their own agree to participate as well. In higher risk research, IRBs may need to request of the investigator some plan for monitoring subject recruitment to ensure that such inducements do not put certain groups of individuals at greater risk.

Although financial compensation for research participation might be considered a potential benefit to subjects, such payment has been the source of much controversy, raising concerns of undue inducement and of the burden of research being assumed by economically disadvantaged populations. FDA has stated that financial compensation should not be considered a benefit in the risk-benefit assessment and that financial compensation should be limited to reimbursement for expenses and inconvenience. For these reasons, many IRBs do not consider monetary compensation as a benefit to be weighed in the risk-benefit relationship (see further discussion below).

In its guidance on “Payment to Research Subjects,”³ FDA (1998) notes that:

Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method

and timing of disbursement to assure that neither are coercive or present undue influence (21 CFR 50.20).

In particular, FDA guidance indicates that payment should be prorated for the time of participation in the study rather than extended to study completion, because the latter could compromise the participant’s right to withdraw at any time.

Because at present there is no practical or theoretical consensus regarding remuneration, sponsors, investigators, and IRBs should closely attend to the ethical and scientific implications of different strategies, particularly regarding payment for incurring risk. Protocols submitted to IRBs should indicate and justify proposed levels and purposes of remuneration that also should be clearly stated in the accompanying consent forms.

F. IRB Review of the Informed Consent Process and Document

The informed consent doctrine states that scientists (or in the context of health care, health care professionals) may not perform invasive tests or conduct studies on individuals without first informing them of the nature of the procedure, including its risks, benefits, and alternatives—as well as possible consequences that might follow the procedures—and obtaining their uncoerced (i.e., voluntary) consent. Thus, informed consent, in its most basic sense, involves a process of communication between a researcher and an individual. The consent process may or may not be punctuated with a signed consent form. (The topic of informed consent is discussed in greater detail in Chapter 12, including the basic elements of consent.) It is the IRB’s duty to determine whether the protocol qualifies for a waiver of the consent requirement and, if not, to review the plans for obtaining informed consent as well as the substance of the consent form.

One of the IRB’s most important activities is evaluating the information to be provided to potential subjects in light of the risks and benefits of the proposed research procedures. Each IRB member brings a different perspective to this review. Certain expert members may be able to correct the technical information or identify omissions in the consent documents provided by the investigators. Other members may add their reactions to the way information is provided or question the adequacy of the information. Whether or not the information is deemed “adequate” depends partly on the impression being conveyed (e.g., whether it is clear that a procedure is to be done for research purposes).

³ See www.fda.gov/oc/ohrt/irbs/toc4.html#payment.

In making a judgment concerning what information should be disclosed in the informed consent process, the IRB should attempt to view the matter from the subject's perspective by asking what facts the subjects might want to know before deciding whether or not to participate in the research. Information could be deemed relevant if it might influence the decision of any reasonable person. For example, the risk of death from cardiac catheterization might be statistically small and, therefore, seem unimportant to an investigator, but it may loom large for those invited to undergo the procedure for the benefit of others. Research in sensitive areas, such as child abuse, illegal activities such as drug or alcohol abuse, or reportable communicable diseases such as HIV, also may pose risks to subjects about which they should be informed. Where the potential for the need to report such information to authorities exists, subjects should be so informed before agreeing to participate in the study. Depending on the circumstances, potential subjects may also feel it is important to be informed about additional costs that might arise during the course of the research, the identity of the research sponsor, any circumstances that would make it difficult or dangerous to withdraw from the research, or the amount or kind of inconvenience involved.

IRBs must ensure that information will be presented to prospective subjects in language they can understand. How well subjects understand that information will vary according to the population from which subjects will be drawn. The medical terms and complex sentences in oral presentations and consent forms often need to be presented in simpler terms, even for the educated layperson. If the prospective subjects include children, persons whose primary language is not English, or populations with the average of a sixth-grade education, the IRB should take special care to ensure that both oral presentations and consent forms are comprehensible to all subjects. Some IRBs find that their lay members are particularly helpful in suggesting necessary modifications. Others ask members of the proposed subject population (e.g., children, clinic patients) to review consent forms and indicate what parts they do not understand.

In addition, the informed consent may not contain any exculpatory language: subjects may not be asked to waive (or appear to waive) any of their legal rights, nor may they be asked to release the investigator, sponsor, or institution (or its agents) from liability for negligence.

It is essential that IRB members think of informed consent not as a form that must be signed but as an educational process that takes place between the investigator and

the prospective subject. No one can guarantee that another person has understood the information presented; one can only inform prospective subjects as clearly as possible. No one can guarantee that another's choice is voluntary; one can only attempt to remove obvious impediments to free choice by being alert to any coercive aspects of the consent procedure. In cases where there is reason for special concern about pressure (e.g., when patients are invited to participate in research conducted by their physicians or when students or employees are asked to participate in research conducted by their teachers or supervisors), the IRB may require some form of monitoring (such as the presence of an impartial observer). If the research presents significant risk, or if subjects are likely to have difficulty understanding the information to be provided, the IRB may suggest that investigators employ devices such as audio-visual aids, tests of the information presented, or consent advisors.

Because obtaining informed consent is an educational process, the IRB should do what it can to enhance the prospective subjects' comprehension of the information presented. It should consider the nature of the proposed subject population, the type of information to be conveyed, and the circumstances under which the consent process will take place (e.g., manner, timing, place, personnel involved). After making these determinations, the IRB may want to suggest changes in the timing or location of an investigator's first contact with potential subjects or changes in how others will contact subjects during or following the study. For example, some investigators may plan to release their data to a "data broker" who will in turn make the data available to other researchers. IRBs should review the appropriateness of making the data available in this way and should ensure that subjects will be informed about who will have access to the data and who might contact them.

Sometimes the information to be imparted to prospective subjects is so complex or possibly disturbing that it may require some time for it to be absorbed and appreciated. In these circumstances, the IRB might suggest that the investigator either present the information and discuss the issues with prospective subjects on more than one occasion or that a period of time be allowed to elapse between imparting the information and requesting a signature on the consent form. During this waiting period, prospective subjects might be encouraged to discuss their possible participation with family members, close friends, or trusted advisors. Other approaches to communicating complex information include the use of audiovisual materials and brochures.

The IRB may waive the regulatory requirement for written documentation of consent in cases where (1) the principal risks are those associated with a breach of confidentiality

oral presentations and consent forms should be comprehensible to all subjects

concerning the subject's participation in the research and (2) the consent document is the only record linking the subject with the research (§____.117(c)(1)). Written documentation of consent may also

**written
documentation
of consent**

be waived when the research presents no more than minimal risk and involves procedures that do not require written consent when they are performed outside of a research setting (§____.117(c)(2); 21 CFR 56.109(c)).

At institutions that require IRB review of all research involving human subjects (including research exempt from the federal regulations), the IRB may decide to waive consent documentation requirements for research that would be exempt from the federal regulations (e.g., most survey and observational research). IRBs taking such an approach should be careful, however, to make sure that the subjects will be provided adequate information about the research. The IRB may decide that, in some cases, subjects should be provided written copies of the information conveyed despite the fact that they are not asked to sign a consent form.

Federal regulations permit modifications in the consent procedure, and under certain circumstances informed consent may be waived entirely if the research meets certain conditions (§____.116(c)-(d)). Such modifications and waivers are not allowed under FDA regulations. The IRB may approve a waiver of some or all of the consent requirements provided that:

**modifications in
the consent
procedure**

- the research involves no more than minimal risk to subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration;
- whenever appropriate, the subjects will be provided with additional pertinent information after they have participated in the study.

Situations in which modification or waiver of consent may be indicated call for careful consideration by the IRB. Decisions to waive informed consent or documentation of informed consent should be clearly documented in the IRB's minutes. Both the National Commission and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research have recommended that such waivers should be granted only if subjects would not be denied benefits or services to which they are otherwise legally entitled.

Sometimes, especially in epidemiological studies, scientists need to review thousands of records to identify appropriate subjects for their study. Consent is not an issue

for record reviews of deceased individuals, because federal regulations apply only to research involving living human subjects (§____.102(f)). It is often difficult, if not impossible, to obtain the permission of everyone whose records are contained in the files. For this preliminary part of the research, IRBs will generally waive the consent requirement if they are satisfied that the information contained in the files is not particularly sensitive; the investigator has devised procedures to protect the confidentiality of the information to be collected; and the study could not practicably be carried out if consent were required. Some university hospitals notify all incoming patients that their records may be reviewed for research purposes; others provide an opportunity to consent (or refuse to consent) to such use.

Contacting potential subjects to obtain further information is a more sensitive phase of the research. IRBs should consider how the investigator proposes to make the initial contact with potential subjects (e.g., through employer, physician, or institution having custody of the records or directly by the investigator) and what information will be conveyed at that time.

In making decisions regarding record reviews and plans for contacting individuals thus identified, IRBs should consider the importance of the research, the extent to which privacy will be invaded, the sensitivity of the information to which the investigators will have access, plans for further contacting the subjects, and the feasibility of obtaining consent from all prospective subjects.

Sometimes, particularly in behavioral research, investigators plan to withhold information about the real purpose of the research or even to give subjects false information about some aspect of the research. This means that the subject's consent may not be fully informed. If the research is to be conducted, some of the consent requirements must be waived. However, the investigator is then obligated to provide the subjects with additional pertinent information after participation (so-called debriefing) (§____.116(d)(4)).

Involving subjects in clinical trials where they may receive a placebo instead of the experimental therapy or where they may not be told which of several treatments they will receive could be said to entail an element of deception. Most commentators now believe that, if subjects are told they may receive a placebo and if the design of the clinical trial is explained to them, no deception is involved.

IRBs reviewing research involving incomplete disclosure or outright deception should apply common sense and sensitivity to the problem. They must first decide whether the information to be withheld would influence the decision of prospective subjects about participating in the research. In the case of research about the effects of background music

on learning and memory, for example, this determination would be relatively easy. According to the regulations, research should not be permitted at all if the risk to subjects is more than minimal and the subjects are not being informed of elements of the research they would consider material to a decision to participate.

A final condition for waiving some or all of the elements of informed consent is that, whenever appropriate, subjects will be given additional pertinent information after they have participated in such a study. The IRB must decide if subjects should be debriefed either after participating in research unwittingly or after knowingly participating in research that involved some form of deception.

Finally, consent is not a single event; rather, it is a process. Because subjects always retain the right to withdraw from a research project, their continuing consent is important. IRBs should be aware that subjects often seem to forget they are involved in research or have difficulty distinguishing research interventions from diagnostic and therapeutic interventions. When a research proposal is first approved, the IRB should determine whether consent should be renegotiated as a formal matter during the course of the research. If renegotiation is required, the frequency and/or events that will trigger this process should be determined and made clear to the investigators.

Federal policy also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research (§____. 116). For example, a totally independent study might find an unanticipated problem in a drug or substance being used in research. IRBs should determine whether any new findings or reports of adverse effects (in the current study or in other studies) should be communicated to subjects. The IRB should also receive copies of any such information that is conveyed to the subjects.

G. IRB Review of the Need for a Data Safety Monitoring Plan

FDA regulations require that protocols submitted under an Investigational New Drug (IND) application include detailed descriptions of the “clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects as to minimize risk” (21 CFR 312.23). In many drug studies this monitoring is undertaken by a Data Monitoring Committee (DMC) or a Data Safety Monitoring Board (DSMB). Such re-

**Data Monitoring
Committee
(DMC) or a Data
Safety
Monitoring
Board (DSMB)**

view bodies are currently used in a variety of situations, and different models of operation have been employed. Although no single model may be optimal for all settings—and there is not necessarily consensus about the optimal model in any given setting—advantages and disadvantages can be described for some of the different approaches that have been taken.

Government agencies that sponsor clinical research, such as the National Institutes of Health (NIH) and the Department of Veterans Affairs, have required the use of DMCs or DSMBs in certain trials. Current FDA regulations impose no requirements for the use of DMCs in trials, except for research studies in emergency settings conducted under 21 CFR 50.24(a)(7)(iv) in which the informed consent requirement may be waived.

In June 1998, NIH issued a policy on data and safety monitoring⁴ that requires oversight and monitoring of all intervention studies to ensure the safety of subjects and the validity and integrity of the data. The policy notes that monitoring should be commensurate with risks and with the size and complexity of the trials.

It is the IRB’s responsibility to assess whether a data safety monitoring plan is needed and to make recommendations to the investigator about the adequacy of the proposed plan. Studies classified as “high risk” would require more intensive and frequent monitoring of data and compliance with human subject protections (see also Chapter 14 for discussion of ongoing review and monitoring after initial review).

In addition, some protocols might involve radiation or biohazards. It is critical that the IRB ensure that appropriate review groups have assessed any safety concerns related to those aspects of the protocol. Chapter 14 describes monitoring in greater detail.

Adverse Events and Unanticipated Problems

FDA regulations and the Common Rule require that adverse events be reported (45 CFR 46.103; 21 CFR 312.56(c),(d); 21 CFR 812.46(b)(1),(2)). The Common Rule requires that any unanticipated problems involving risks to subjects or others be reported to the IRB of record (§____.103(5)), and FDA regulations contain requirements for the reporting of adverse events during all phases of product development as well as some post-approval reporting requirements (21 CFR 312.32(a) and 21 CFR 812.2(s)). (Chapter 14 provides an extensive discussion of IRB review of unanticipated problems or adverse events.)

⁴ See <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

H. Frequency of Review

IRB responsibility for assessing risks and potential benefits does not end with the initial approval of the research protocol. The Common Rule at §____.103 and FDA regulations at 21 CFR 56.108(b) require institutions to establish written procedures for the “prompt reporting to the IRB of any unanticipated problems involving risks to subjects....” Sponsors of FDA-regulated research are required to “notify FDA and all participating investigators in a written IND safety report of any adverse event associated with use of the drug that is both serious and unexpected” (21 CFR 312.32(c)). Although this regulation does not require the sponsor to notify IRBs at participating study sites, it is routine for sponsors either to instruct investigators to provide a copy of the safety report to the IRB or to send a copy of the report directly to the IRB.

Thus, greater than minimal risk studies, in which risks are anticipated, require that IRBs reassess the risk-benefit relationship of the research as it proceeds and more information becomes available. These additional reviews might result in modifications to the consent form, the reconsent of current subjects, or modification of the research plan to reduce risk. The IRB can also terminate the study if new information negatively alters the risk-benefit ratio, although increasingly this decision is made by a DMC or DSMB, if the study has one.

At a minimum, IRBs are also required by regulation to conduct periodic continuing review of approved protocols “at intervals appropriate to the degree of risk, but not less than once per year” (§____.109(e)). The criteria for IRB reapproval are the same as for initial review, including the requirement that the risks to subjects are minimized and reasonable in relation to anticipated benefits. Therefore, continuing review of ongoing research requires the IRB to identify any changes in the risk profile of the research, as well as to reassess the potential benefits of the research.

periodic continuing review

At the time of the initial review, the IRB should inform the investigator of ongoing reporting requirements. These requirements include the following responsibilities:

- The principal investigator (PI) should submit to the IRB a progress report with proposed modifications to the protocol for review and approval prior to implementing the modifications.
- The PI should notify the IRB administrator and submit a report concerning all incidents of injury and other unanticipated problems involving risks experienced by subjects.

- The PI of expedited and full review research should submit to the IRB a progress report annually or more frequently if the risk to subjects is more than minimal or if the IRB deems closer monitoring advisable. The informed consent document should be submitted with the progress report for all ongoing research. All projects deemed to be “exempt from review” do not require an annual update, but they will require notification if the protocol is modified in order to verify continued exempt status.

Between IRB reviews, it is largely the researchers’ responsibility to keep the IRB informed of significant findings that affect the risk-benefit ratio. In larger studies or clinical trials, a DMC/DSMB may be responsible for keeping the IRB up to date.

I. Compliance with All Applicable State Laws

IRBs must be cognizant of local laws and regulations governing research at their institutions or in their states. For example, age of majority is the legal age established under state law at which an individual is no longer a minor and, as a young adult, has the right and responsibility to make certain legal choices that adults can make. In some states there may be additional laws and procedures that allow for a lesser determination of competency for specific purposes, such as competency for providing informed consent. States might have different statutes concerning legally authorized representatives of minors or decisionally impaired persons—for example, first-degree relatives, parents, or, if the parent is not available, a guardian or surrogate. Finally, states might vary on the legality of certain types of research (e.g., embryo research, end-of-life research) and on privacy protection. It is incumbent on the IRB to be aware of these local requirements.

Key Concepts: Minimal Regulatory Requirements for IRB Review

Regulatory Review Requirement	Suggested Questions for IRB Discussion
<ul style="list-style-type: none"> The proposed research design is scientifically sound and will not unnecessarily expose subjects to risk. 	<ul style="list-style-type: none"> Is the hypothesis clear? Is it clearly stated? Is the study design appropriate to prove the hypothesis? Will the research contribute to generalizable knowledge, and is it worth exposing subjects to risk?
<ul style="list-style-type: none"> Risks to subjects are reasonable in relation to anticipated benefits, if any, and to the importance of knowledge that may reasonably be expected to result. 	<ul style="list-style-type: none"> What does the IRB consider the level of risk to be? What does the PI consider the level of risk/discomfort/inconvenience to be? Is there prospect of direct benefit to subjects?
<ul style="list-style-type: none"> Subject selection is equitable. 	<ul style="list-style-type: none"> Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for inclusion/exclusion addressed)? Seriously ill persons? Healthy volunteers? Are these subjects appropriate for the protocol?
<ul style="list-style-type: none"> Additional safeguards are provided for subjects likely to be vulnerable to coercion or undue influence. 	<ul style="list-style-type: none"> Are appropriate protections in place for vulnerable subjects—for example, pregnant women, fetuses, socially or economically disadvantaged persons, decisionally impaired persons?
<ul style="list-style-type: none"> Informed consent is obtained from research subjects or their legally authorized representatives. 	<ul style="list-style-type: none"> Does the informed consent document accurately convey anticipated risks and potential benefits? Is the consent document understandable to subjects? Who will obtain informed consent (PI, nurse, other) and in what setting? If appropriate, is there a children's assent? Is the IRB requested to waive or alter any informed consent requirement?
<ul style="list-style-type: none"> Risks to subjects are minimized. 	<ul style="list-style-type: none"> Does the research design minimize risks to subjects? Would use of a DSMB or other research oversight process enhance subject safety?
<ul style="list-style-type: none"> Subject privacy and confidentiality are maximized. 	<ul style="list-style-type: none"> Will personally identifiable research data be protected from access or use to the extent possible? Are any special privacy and confidentiality issues properly addressed, such as the use of genetic information?
<p>Additional Considerations</p>	
<ul style="list-style-type: none"> Ionizing radiation 	<p>If ionizing radiation is used in this protocol, is it medically indicated or for research use only?</p>
<ul style="list-style-type: none"> Biohazards 	<p>Does the research involve biohazardous agents for which additional oversight or protection is warranted?</p>
<ul style="list-style-type: none"> FDA-regulated research 	<p>Is an IND or Investigational Device Exemption involved in this protocol?</p>
<ul style="list-style-type: none"> Applicable state laws 	<p>Does the research comply with all applicable state laws?</p>

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Chapter 12

Recruitment of Subjects and the Informed Consent Process

- A. Introduction
 - B. Recruitment of Subjects
 - C. The Elements of Informed Consent
 - D. What Should Be Disclosed in the Consent Process?
 - E. Enhancing Comprehension
 - F. The Obligation to Develop an Informed Consent Process
 - G. Special Requirements for Children Involved as Subjects in Research
 - H. Waiver of Informed Consent
 - I. Documentation of Informed Consent
 - J. Consent/Permission Authorized by Others
- Key Concepts**
References



A. Introduction

The *Belmont Report: Ethical Principles and Guidelines in the Protection of Human Subject of Research (Belmont Report)* sets forth three ethical principles governing human research: respect for persons, beneficence, and justice (National Commission 1979). The principle of respect for persons requires:

1. that individuals are treated as autonomous agents; and
2. that persons with diminished autonomy are protected.

An autonomous agent is “an individual capable of deliberation about personal goals and of acting under the direction of such deliberation” (National Commission 1979, 5). Respect for persons requires that prospective research subjects “be given the opportunity to choose what shall or shall not happen to them” and thus necessitates adequate standards for informed consent (National Commission 1979, 10). At its most basic, informed consent must be effective and it must be prospectively obtained. The informed consent process involves the following three elements:

1. Disclosing information to potential research participants
2. Ascertaining that they understand what has been disclosed
3. Ensuring their voluntariness in agreeing to participate in research (Faden and Beauchamp 1986)

Research begins with the recruitment and selection of potential subjects. The selection of research subjects addresses the principle of justice—that is, ensuring that there is fairness in the distribution of benefits and burdens from the research. Consequently, justice is gained by fair and appropriate recruitment of subjects into research, and respect for persons is upheld by communicating to potential subjects the information a rational person would want to have in order to decide whether to participate in a research project.

From an ethics perspective, the informed consent process is the critical communication link between the prospective research subject and the investigator, beginning with the initial approach of the investigator to the potential subject (e.g., a flyer, brochure, or any advertisement regarding the research study) and continuing until the end of the research study. It should be an active process of sharing information by both parties throughout which the subject at any time is able to freely decide whether to withdraw or continue participating in the research. The consent form, if there is one, is intended only to document the interaction between the subject and the investigator, and it is only one part of the informed consent process. Thus, increasingly, discussions about informed consent have focused on its importance as a process, with

**informed
consent
process**

the goals of ensuring that information is fully disclosed and that competent individuals fully understand the research so that they can make informed choices.

These ideals are more difficult to achieve in practice, however, because of the complexity of some types of research, the wide disparities among individuals regarding their ability to comprehend and process complex information, and the tendency of some institutions to consider the informed consent document mainly as a legal record for the purposes of future liability. As a result, empirical evidence suggests that the regulatory and legal environment frequently results in failures to achieve voluntary informed consent (Verheggen et al. 1996; Waggoner and Mayo 1995).

This chapter discusses the appropriate recruitment of subjects into research—which some consider to be the first stage of the consent process—the substantive and procedural requirements of the informed consent process, the regulatory requirements and when they may be waived, and specific consent issues concerning children or those who are decisionally impaired. A special consent exception with unique requirements is the case of research on emergency medical care, an area of research that is discussed in Chapter 16 of this resource manual.

B. Recruitment of Subjects

An ongoing challenge for researchers is the recruitment of adequate numbers and types of individuals in research. This is a particular challenge for large clinical trials that require significant numbers of subjects in order to achieve sufficient statistical power. Thus, some investigators must aggressively pursue various strategies to recruit and enroll subjects in research to answer the research questions being posed. Under federal regulations, the Institutional Review Board (IRB) must review and approve the methods used to recruit subjects in order to ensure that the methods are not coercive or unduly influencing and that the confidentiality and privacy of potential subjects are protected (see also Chapter 11 for a discussion of the IRB's role in reviewing plans for recruitment; §___ .111(a)(3); 21 CFR 56.111(a)(3)). Every protocol should include a recruitment section that clearly describes the following:

- how potential subjects are identified
- how and by whom subjects are approached about participation
- when consent is obtained in relation to the start of the study procedures
- whether third parties (e.g., “data brokers,” calling centers/centralized screening centers) will assist with the recruitment of subjects

Methods for Identifying Subjects

IRBs should review how potential subjects will be identified in order to ensure that their confidentiality is protected and that selection is equitable. Subjects with specific diseases or conditions are often identified as potential subjects through some type of record (e.g., registries, physician or hospital records, employment or school records). Control groups might consist of individuals in the same subpopulation as the subjects (which would be the case in a randomized clinical trial), those with unrelated conditions, or healthy volunteers from the general population. If potential subjects are identified through medical records, log books, physicians' records, or other records that are not public documents, the IRB should make certain that the following conditions have been met: (1) the investigator is allowed access to such records by the institution or the physician and (2) responsibility for confidentiality and protection of privacy is clearly accepted by the investigator (see also Chapter 13 for an extensive discussion of the Privacy Rule).

Records Screening

Sometimes it might be necessary for an investigator to review thousands of medical records to identify a small number of subjects who are suitable for a study. Such “screening” procedures have been a topic of confusion, with uncertainty about the role of the IRB and the need for consent from individuals whose records might be perused.

Procedures that are to be performed as part of the practice of medicine and that would be done regardless of whether research participation was subsequently contemplated—such as for diagnosis or treatment of a disease or medical condition—may be performed and the results subsequently used for determining study eligibility without first obtaining consent for such screening. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research. When a physician-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Screening procedures for determining research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure, the IRB may choose to use expedited review procedures (see Chapter 10). The

**screening
procedures for
determining
research
eligibility**

IRB should receive a written outline of the screening procedure that is to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing them, including a brief description of the study in which subjects may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

One alternative to a broad screening approach may be the use of a data broker, an intermediary who already has access to the data. The broker can review records to identify appropriate subjects, whose consent to participate in the study can then be sought. With auto-mated record-keeping systems, it may be easier to identify appropriate subjects without reviewing all the records. IRBs will have to decide under what conditions a researcher may scan thousands of medical or other private records while searching for a small number of appropriate subjects. One factor to consider would be the sensitivity of the information likely to be contained in the records (for example, Did the patients have broken legs or abortions? Were they treated for influenza or sexually transmitted diseases?) Another factor to consider is the type of information the researcher wishes to obtain from those who are selected as suitable subjects for the study. Thus, in reviewing plans for screening records to identify potential research subjects, IRBs must be cognizant of privacy concerns and the risks that might accompany disclosure of confidential and potentially sensitive information. In general, the Principal Investigator should not contact the potential recruits regarding screening; such an activity should be conducted by a data broker or some other neutral third party.

data broker

Use of Advertising for Recruitment Purposes

The use of advertising to recruit research subjects is not, in and of itself, an objectionable practice. When advertising is to be used, however, IRBs should review the information contained in the advertisement, as well as the mode of its communication, to determine whether the procedure for recruiting subjects affords adequate protection.

Posters, brochures, mailings, and newspaper advertisements are all legitimate methods to inform people of studies they might be interested in joining and are not in and of themselves considered objectionable recruitment practices (OPRR 1993). IRBs should review advertising to assure that

it is not unduly influencing and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. Thus, IRB review is necessary to ensure that the information is not misleading to subjects, especially when a study will involve persons with acute or severe physical or mental illness or persons who are economically or educationally disadvantaged. The IRB should review the final copy of printed advertisements to evaluate not only the verbal content but the relative size of type used and other visual effects.

advertisements should be reviewed and approved by the IRB

The Food and Drug Administration (FDA) considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study.

When advertisements are to be taped for broadcast, the IRB should review the final audio-/videotape. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB may wish to caution the clinical investigators to obtain IRB approval of message text prior to taping to avoid re-taping because of inappropriate wording.

When advertisements are easily compared with the approved consent documents, the IRB chairperson or other designated IRB member may review and approve by expedited means, as provided by §____.110(b)(2) and 21 CFR 56.110(b)(2). When the IRB reviewer has doubts about the wording of the advertisement or its dissemination, or when other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

C. The Elements of Informed Consent

Voluntary, informed consent to participate in research has been an ideal to which researchers and others have aspired for more than half a century. As stated in the *Nuremberg Code*, the voluntary consent of the human subject is absolutely essential:

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and

comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity (Nuremberg 1949).

There are both substantive and procedural requirements for obtaining informed consent. Much of this information is specified in the federal regulations.

substantive and procedural requirements for informed consent

Federal Regulatory Requirements

Federal regulations permit IRBs to approve research when informed consent is sought and documented from each prospective participant (§____.111(a)(4),(5); 21 CFR 56.111(a)(4),(5)). (Requirements for informed consent are further described in the regulations at §____.116 and _____.117 and 21 CFR 50.20, 50.25, 50.27, 56.109.) There are substantial differences between the Common Rule and FDA requirements regarding a waiver of consent, the most notable being that the FDA regulations do not contain the criteria for waiver or alteration of informed consent as described at §____.116(d).

The current regulatory system specifies eight basic elements of information disclosure that must be provided to prospective participants during the informed consent process, except in cases of an approved waiver or alteration of the consent process by the IRB (described below). Even when some direct benefit to participants may be anticipated, these high standards for disclosure should be met, because research inherently involves uncertainty. The basic elements of informed consent are as follows:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental

2. A description of any reasonably foreseeable risks or discomforts to the subject
3. A description of any benefits to the subject or to others that may reasonably be expected from the research
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
6. For research involving more than minimal risk, an explanation regarding whether any compensation is available and an explanation regarding whether any medical treatments are available if injury occurs, and, if so, what these consist of or where further information may be obtained
7. An explanation of whom to contact for answers to pertinent questions about research and research subjects' rights and whom to contact in the event of a research-related injury to the subject
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (45 CFR 46.116(a); 21 CFR 50.25(a)).

FDA regulations differ in requiring an additional statement that FDA may inspect records

Although it is tempting to require a set of basic elements of disclosure to be used during the informed consent process, it is unlikely that any single set of basic elements can be applied feasibly and credibly to all types of research. Whether an investigator has included the eight basic elements of disclosure is often open to interpretation. For example, some clinical research includes the possibility that a subject might be assigned to a control (or placebo) group. Although it is incumbent on the investigator to ensure that the potential subject understands this as a possibility, it also makes it difficult for the investigator to disclose with any certainty what the actual risks and potential benefits might be. If the study design truly achieves equipoise—that is, the risks and potential benefits are in fact unknown—then the investigator in good conscience can describe the uncertainties of the proposed research.

D. What Should Be Disclosed in the Consent Process?

Also specified in the federal regulations are six additional elements of disclosure, as follows, that must be included when appropriate (§____.116(b); 21 CFR 50.25(b)):

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
3. Any additional costs to the subject that may result from participation in the research
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
6. The approximate number of subjects involved in the study

However, as noted in the *Belmont Report*, "a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided" (National Commission 1979, 4). It is the IRB's job to determine whether what will be disclosed is sufficient. The National Commission suggested that IRBs use the standard of "the reasonable volunteer," that is, "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge" (1979, 4). Communicating risks is always difficult, as they are interpreted subjectively. Likewise, the anticipation of benefits, whether a real possibility or wishful thinking, is difficult to assess and control.

disclosure appropriate for the reasonable volunteer

Even when the informed consent process makes it clear that there is no anticipation of direct benefits to subjects, there will always be some individuals who hold out the prospect that this might not be the case for them. Nonetheless, it is critical that the informed consent process makes clear, in no uncertain terms, the likelihood and magnitude of risks and the prospects, or lack thereof, of potential benefits.

Compensation for Research-Related Injury

The Common Rule requires only that when research involves more than minimal risk, information should be disclosed regarding whether medical treatment and other compensation will be provided for research-related injuries. Many critics of the policy of the United States believe that there should be more than disclosure of information about compensation, and they call for the provision of medical care for research-related injuries without cost to the research subjects and, in addition, for compensation for lost wages, disabilities, and death. These claims are based on the belief that research subjects, whatever their motivations, accept

risk on behalf of society. When subjects are injured, justice, fairness, and gratitude mandate, at a minimum, the provision of needed medical treatment without cost to the individual. Some funding agencies (for example, the Department of Veterans Affairs) require this through regulation (38 CFR 17.85).

In its 2003 report, *Responsible Research: A Systems Approach to Protecting Research Participants*, the Institute of Medicine compiled a list of questions that a potential research subject might want to ask before volunteering for research (see Table 12.1). These questions provide a helpful guide for investigators and IRBs in judging the adequacy of the consent process.

E. Enhancing Comprehension

The emphasis on disclosure in informed consent is a product of a legal and regulatory environment that equates informed consent solely with the requirements to disclose information (Beauchamp and Childress 1994). This emphasis is not, however, fully conducive to the more comprehensive view of an informed consent process, which emphasizes the aspects of understanding, capacity to consent, voluntariness, and features of decisionmaking, including who may authorize consent (Beauchamp and Childress 1994; Faden and Beauchamp 1986).

To enhance comprehension of the information disclosed in the consent process, its presentation must be adapted to the potential subjects' capacities and characteristics, and great care must be taken to ascertain that the prospective subjects understand the information. Extra efforts may be warranted to verify comprehension when risks are especially high or when there is uncertainty regarding whether the prospective subjects are capable of understanding the risks.

The information must be in language that subjects can readily understand and must be as brief as possible while still being sufficiently comprehensive to provide the needed knowledge. The information must be delivered in such a context that subjects can readily evaluate it, deliberate, ask questions, discuss issues, and reach a considered decision. To ensure comprehension, the presentation of information must be adapted to the potential subjects' capacities and characteristics, and care must be taken to ascertain that the prospective subjects understand the information.

Extra efforts might be warranted to verify comprehension when risks are especially high or when there is uncertainty regarding whether the prospective subjects are capable of understanding the risks. It is important to respect those who are not autonomous persons (e.g., young children, the

Table 12.1**What a Participant Might Want to Know****Potential Benefits and Harms**

- If I am ill, will this research help me?
- What are the risks to me?

Protecting Participant Interests

- What are the realistic alternatives to study participation?
- What is involved? What will I have to do?
- Who will be in charge of my care? Can I see my own doctor?
- Are checks and balances in place to protect my safety?
- How was the research reviewed and approved?
- Will I be charged anything or be compensated for my participation?
- How can I end my participation if I change my mind?
- What will happen to me when the study is over? Will I be told the results?

Study Design and Leadership

- Who designed the protocol?
- Is the protocol well designed?
- Is the investigator competent?
- Why is this research important?
- Who else is involved in this research?
- Was anyone in the advocacy community involved in the design or review of the research?

Conflict of Interest, Study-Related Controversy

- Is the study controversial?
- Has anyone conducted this study already, or one like it?
- Who will benefit financially if this works? What's in it for the investigator?

Institutional Oversight

- Whom do I contact to express concerns to or obtain information from?

SOURCE: (IOM 2003). The information in this box was supplemented by elements described in the Department of Veterans Affairs' booklet, *I'm a Veteran: Should I Participate in Research?*

mentally ill) by providing an appropriate explanation of risks, if possible, and conducting an appropriate process to seek the approval of next of kin or legally authorized representatives.

Assessing whether a subject is sufficiently informed to make a decision is an essential part of the consent process; however, conducting such an assessment can be difficult. In general, it is useful to assess the success of the informed consent process in terms of understanding rather than in terms of the successful conveyance of information. Truly informed consent means that the subject appreciates the significance of the information and its applicability to his/her circumstances. Thus, content-based assessments do not necessarily indicate a subject's comprehension, because the same information is received and processed differently by different people.

For example, studies of risk communication in genetic research testing for cancer susceptibility confirm that individuals with some family history of cancer tend to overestimate their risk and that these perceptions of personal risk are often resistant to standard education and counseling approaches (Croyle and Lerman 1999). Other studies in genetics have found that socioeconomic status affects the informational priorities of women, with women in lower socioeconomic groups commonly believing that genetic susceptibility testing in the research setting is a means for diagnosing cancer (Bernhardt et al. 1997). Thus, factors that influence the amount and type of information that subjects want or need are self-perceived risks and self-perceived benefits.

Other studies have shown that understanding the uncertainties of research is not always achieved. For

example, some subjects have considerable difficulty differentiating between a particular physician-investigator lacking certain knowledge and that knowledge simply not existing. In addition, subjects tend to overestimate the benefits of research and tend either to not understand or to disregard information relating to its limits. This can result in unrealistic expectations.

Some research subjects, particularly if they are also patients, might be confused about the differences between research and therapy. They might think that they are receiving treatment designed by a physician with their best interests in mind, when in fact the activity is driven by the demands of science. This phenomenon, referred to as the *therapeutic misconception*, can—despite meaningful disclosure by the investigator—induce an individual to participate in research because he/she is hoping for a therapeutic benefit. Physicians might share this hope as well and hold somewhat unrealistic expectations of therapeutic benefits for their patients. Moreover, it cannot be ignored that in some cases access to an experimental protocol might, in fact, provide access to high-quality care that otherwise likely would not be available. Nonetheless, ensuring that subjects understand the limits of any potential benefits is an important element of comprehension.

Investigators and IRBs must be mindful of the expected limitation of comprehension, including language or cultural barriers and educational attainment. The cultural norms and lifestyles of subjects should be considered in deciding how to approach informed consent. The culture and context of the research should dictate whether to present material in printed form, recruit and inform individually or in groups, or seek the consent of gatekeepers or superiors in lieu of, or in addition to, individual consent. It is disrespectful to treat persons in ways that are incompatible with their cultures and circumstances. In light of this, it increasingly is the practice of some researchers to consult with the relevant communities in the design, conduct, and consent process employed in research.

Those who are functionally illiterate, those who are suspicious of persons who proffer documents or require signatures, and those from traditional cultures also should be approached in the style that is most comfortable for them. Protocols for research on such populations should show evidence that the researcher is informed about the culture of the intended research population and has arranged the informed consent and other research procedures accordingly.

Studies looking at comprehension regarding consent have demonstrated that level of educational attainment (a proxy measure for socioeconomic status) affected “knowledge scores” (Bernhardt et al. 1998). People with more formal education scored higher and were able to use printed

materials to augment the session. Those who were less well educated might require additional sessions and approaches to sufficiently comprehend the information.

The need for assessment of comprehension varies across the spectrum of tests. It can range from the request for a verbal affirmation from the subject (for example, Do you understand or have any questions?) to the need to actually ask specific questions of the subject to determine whether he/she comprehends the information provided and can process it within the context of his/her situation.

IRBs should be flexible in considering as wide a range of media as possibly appropriate for disclosing the information required for the consent process. The use of videotapes, brochures, group discussions, Web sites, community newsletters, and other community-based outlets (e.g., schools, religious organizations) can be more appropriate methods for communicating with potential subjects than the use of legalistic formal consent forms. Having established an effective means of informing potential subjects and having given them the appropriate context and time to consider their decision, a brief verbal discussion may suffice to ensure that critical details have been considered and all questions have been answered. The emphasis should be on effective communication with the appropriate opportunity for exploring, asking questions, achieving clarity and understanding, reflecting, and making reasoned decisions.

methods for enhancing comprehension

E. The Obligation to Develop an Informed Consent Process

The informed consent process should involve an exchange that provides a rational basis for subjects to make informed and sound decisions about participation. Subjects should have a comfortable context in which to think about what they have been told and to ask any questions that occur to them. The importance of clear and appropriate communication goes beyond respecting the autonomy of subjects. Such communication has powerful implications for motivating subjects to participate with integrity and trust, sustaining their participation through possibly long-term or longitudinal studies, and facilitating the provision of valid data.

ensure voluntariness

A central goal of the informed consent process is to ensure voluntariness—that is, to ensure that an agreement to participate in research is valid only if voluntarily given. Thus, the process and the offering of consent must take place under conditions free of coercion and undue influence. In the words of the *Belmont Report*:

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable (National Commission 1979).

In reviewing the plan for obtaining informed consent, investigators and IRBs must be sensitive to the possibility that potential subjects might feel pressure to participate when those seeking consent are in positions of authority or of commanding influence (e.g., physicians, professors, employers). IRBs that are concerned about the possibility that potential subjects might feel pressured to participate or might lack the ability to fully comprehend the risks and potential benefits can require that the consent process be monitored.

Consent Monitoring

In certain circumstances, monitoring the informed consent process could increase subject protection, and monitoring procedures could be used to measure subjects' understanding of the nature of the research and the risks involved. Such circumstances might include research involving significant risk, research enrolling participants who might have difficulty in understanding the risks associated with the study, or research for which the IRB has concerns regarding whether the informed consent is being carried out according to the stipulations in the approved protocol. In these cases, IRBs might require some type of monitoring of the informed consent process, although the IRB need not perform the monitoring itself. These mechanisms could be either temporary, lasting until the concerns of the IRB are satisfied, or permanent, for the duration of the research study.

Consent as an Ongoing Process

Research participation involves time and possibly some inconvenience and discomfort. An adequate informed consent process can differentiate individuals who might more easily participate from those who might not or who might wish to opt out for good reason. There are many kinds of minor or everyday risks or inconveniences that most people would gladly undertake if it were their choice to do so but that they would not wish to have imposed unilaterally on them. Alternatively, given a clear understanding of what would be involved in the research, some may make a

**option to
withdraw from
the study**

rational decision that the experience would be too stressful, risky, or unpleasant for them for some specific reason that applies to them and not necessarily to other subjects.

When the research procedure is long and complex, the researcher must make it clear that the subject is free to ask questions at any time and has the option to withdraw from the study without providing a justification to the investigator. Informed consent, as a conversation, needs to be available throughout the research project, as subjects do not necessarily develop questions or concerns about their participation until they are well into the research experience. For example, a discussion of confidentiality may not capture subjects' attention or comprehension until they are asked personal questions in the ensuing research experience. At that point the subject should feel free to satisfy those questions about confidentiality. Naturally, the consent process will differ depending on the risk of the research.

Reconsent

Occasionally, as facts emerge from a study, the investigator chooses to modify the protocol design or the intervention. Such changes to protocol must be presented to the IRB. If, upon review of the modifications, the IRB determines that the risk-benefit calculus has changed, requiring a modification to the consent procedure, the investigator must go back to the research subjects to update and reconfirm their willingness to continue as subjects.

G. Special Requirements for Children Involved as Subjects in Research

For Department of Health and Human Services (DHHS) supported or DHHS-conducted research or for any other agency that has adopted the children's regulations, Subpart D of 45 CFR 46 contains special provisions for consent and assent when children are the subjects of research (see Chapter 21 for a more extensive discussion regarding research with children). The regulations require that the IRB determine, as follows, whether:

...adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children, and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research (45 CFR 46.408(a)).

However, even if the IRB determines that the subjects are capable of assenting, it can still waive the assent requirement under specific circumstances, in accordance with the waiver criteria of Subpart A.

Subpart D states that the IRB may find that the permission of *one* parent is sufficient for research to be conducted. Where research is considered acceptable, according to the regulations, and permission is to be obtained from parents (as determined by the IRB), *then both parents must give their permission*, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement in order to protect the subjects (e.g., neglected or abused children), it may waive the consent requirements in Subpart A, provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted and provided further that the waiver is not inconsistent with federal, state, or local law.

H. Waiver of Informed Consent

The federal regulations recognize that circumstances arise in which the requirement of seeking informed consent from competent participants may be waived, but they stipulate that *all* of the following four criteria must be met to waive informed consent:

**four criteria
must be met to
waive informed
consent**

1. The research involves no more than minimal risk to the subjects
2. The waiver will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participating (§____.116(d); 21 CFR 50.23, 50.24)

The FDA regulations only provide for waiver of informed consent in limited emergency situations.

The third and fourth stipulations are sometimes difficult to interpret, because the word *practicably* is subjective and contextual. Because IRBs often interpret “could not practicably be carried out” to mean impossible to carry out, they require the element of disclosure to be included, often in a less than meaningful way (NBAC 1999).

In general, waiver of the informed consent process is justifiable in research studies in which there is no interaction

between investigators and participants and risks are minimal, such as in studies using existing identifiable data (e.g., studies using medical records) for which adequate protections are in place. Many steps can be taken to protect both privacy and confidentiality (e.g., use of coding or data brokers), and, with such protections in place, IRBs may waive the requirement for informed consent.

FDA has two exceptions from the general requirements for informed consent. The regulations at 21 CFR 50.23 provide an exception for research where the subject is confronted by a life-threatening situation necessitating the use of the test article. This so-called emergency research waiver allows, under specific conditions, research to proceed without consent if the subject is unable to communicate or provide legally effective consent. This exception can apply only in cases where an IRB has reviewed procedures and there has been a process of community consultation and public disclosure (requirements for emergency research are discussed in greater detail in Chapter 16).

The other exception granted by FDA relates to the President’s authority under 10 USC 1107(f) to waive the requirement for prior consent for the administration of an investigational new drug to a member of the armed forces in connection with the member’s participation in a particular military operation. (This exception to the FDA requirements for informed consent is discussed in greater detail in Chapter 16.)

I. Documentation of Informed Consent

The federal regulations are quite specific in requiring that informed consent be documented by the use of a written consent form approved by the IRB and signed by the subject or his/her legally authorized representative (§____.117(a); 21 CFR 50.27(a)). The FDA regulations differ from the Common Rule in requiring that the form be dated at the time the consent form is signed.

The regulations state that documentation of consent can include the following:

- A written consent document that embodies the elements of informed consent required by §____.116. This form may be read to the subject or the subject’s legally authorized representative, but in any event, the investigator should give either the subject or the representative adequate opportunity to read it before it is signed
- A short form written consent document stating that the elements of informed consent required by §____.116 have been presented orally to the subject or the subject’s legally authorized representative. When this method is used, there should be a witness to the oral presentation. In either case, the IRB must approve a

written summary of what is to be said to the subject or the representative

An IRB can waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the consent document, and the principal risk would be any potential harm resulting from a breach of confidentiality. Each subject should be asked whether he/she wants documentation linking him/her with the research, and the subject's wishes should govern
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. In any case, the investigator is not authorized to make the decision to waive the documentation requirement without IRB approval.

J. Consent/Permission Authorized by Others

For individuals with “diminished autonomy” (e.g., children), informed consent procedures typically involve obtaining consent from an individual who has the legal authority to make decisions about the individual's participation in research, but special provision may need to be made when comprehension is severely limited—for example, by mental disability. Even for these individuals, however, respect requires giving them the opportunity to choose, to the extent that they are able, whether or not to participate in research. In the words of the *Belmont Report* (National Commission 1979), “such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.” Individuals chosen to permit participation on behalf of others should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. Moreover, the person authorized to act on behalf of the subject should be provided

with the opportunity to observe the research as it proceeds to be able to withdraw the subject from the research, if such action appears to be in the subject's best interest.

The Common Rule uses the phrase *legally authorized representative* to describe an individual who has the authority to consent on behalf of another individual for medical care or research participation. State laws usually contain general provisions on the standards and procedures governing appointment of guardians for persons declared legally incompetent to make their own decisions. However, relatively few states have laws specifically addressing *research* decisionmaking by legal guardians or other allowable surrogates. Moreover, existing legislation in some states limits the involvement of incapable subjects in research in various ways.

A number of state laws, for example, require guardians to obtain specific court authorization to make decisions

**legally
authorized
representative**

on a ward's participation in a research protocol. In addition, several states currently prohibit certain types of research on persons with mental disorders, particularly research that presents greater than minimal risk and from which subjects are not intended to benefit (NBAC 1998).

It is the duty of the investigator and the IRB to be knowledgeable about applicable state laws. In addition, when someone other than the subject is consenting to research participation, the IRB might choose to invoke certain protections, including additional monitoring of the study, requiring a consent auditor, or requiring educational activities for authorized representatives. In states lacking a clear law, it might be left to federal policy, investigators, and IRBs to determine who, if anyone, may act as a surrogate decisionmaker for a person who lacks decisional capacity. At present, legal guardianship is rarely, if ever, sought in the research setting. Instead, close family members, who may or may not have formal guardianship status, are the customary decisionmakers when the research participation of incapable adults is sought.

Key Concepts:

Recruitment of Subjects and the Informed Consent Process

- At its simplest, informed consent must be effective and prospectively obtained. The informed consent process involves three elements: (1) disclosing information to potential research participants; (2) ascertaining that they understand what has been disclosed; and (3) ensuring their voluntariness in agreeing to participate in research.
- Under federal regulations, the IRB must review and approve the methods used to recruit subjects to ensure that the methods are not coercive or unduly influencing and that the confidentiality and privacy of potential subjects are protected.
- When advertising is to be used, IRBs should review the information contained in the advertisement, as well as the mode of its communication, to determine whether the procedure for recruiting subjects affords adequate protection.
- The current regulatory system specifies eight basic elements of information disclosure that must be provided to prospective participants during the informed consent process, except in cases of an approved waiver or alteration of the consent process by the IRB.
- The consent form, if there is one, is intended to document the interaction between the subject and the investigator, and it is only one part of the informed consent process.
- Clinical screening procedures for determining research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight.
- The Common Rule requires only that when research involves more than minimal risk, information should be disclosed regarding whether medical treatment and other compensation will be provided for research-related injuries. Specific departments and agencies may have other requirements, however.
- To enhance comprehension of the information disclosed in the consent process, its presentation must be adapted to the potential subject's capacities and characteristics, and great care must be taken to ascertain that the prospective subject understands the information.
- In certain circumstances, monitoring the informed consent process could increase subject protection and monitoring procedures could be used to measure the subject's understanding of the nature of the research and the risks involved.
- Where research with children is considered acceptable and according to the regulations and permission is to be obtained from parents, both parents must give their permission, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child.
- The federal regulations recognize that circumstances arise in which the requirement of seeking informed consent from competent participants may be waived, stipulating four criteria that must all be met to waive informed consent.
- FDA has two exceptions to the informed consent requirement: emergency research and a Presidential waiver when an investigational new drug is administered to a member of the armed forces involved in a particular military operation.
- The federal regulations are specific in the requirement that informed consent be documented by the use of a written consent form approved by the IRB and signed by the subject or his/her legally authorized representative. FDA regulations differ from the Common Rule in requiring that the form be dated at the time the consent form is signed.

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Chapter 13

Privacy and Confidentiality

- A. Introduction
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A. Introduction

Research relies on the efficient acquisition, analysis, and transfer of data that are accurate, readily accessible, and maintained with integrity. Protecting the privacy of individual subjects and the confidentiality of the data is the responsibility of all data users and is necessary to protect individual rights and public expectations.¹ This protection is especially important because some individuals may refuse to seek medical care or to participate in research because they fear exploitation or loss of privacy.

Federal and state laws and regulations protect the confidentiality of some medical information, while other rules address privacy and confidentiality in the context of protecting research subjects from risks of harm.² Potential harms from inappropriate disclosures of personal information include anxiety or emotional distress/psychosocial harm; violation of individual rights of autonomy (including the right not to know certain information or unwanted self-revelation, e.g., in the Milgram study); social harm (e.g., familial conflict, inability to

marry, stigmatization); the more general risks associated with the receipt of unvalidated research data; economic harm, such as loss of employment or insurability; or legal harm (civil or criminal penalties).

This chapter will examine the protection of privacy and confidentiality in the context of research and the legal, regulatory, and ethical standards for such protection.

B. Identifying, Evaluating, and Mitigating Risks to Privacy and Confidentiality in the Conduct of Research

Identifiable Data

Depending on the amount and type of clinical, familial, and personal information retained, research data may be anonymous (completely stripped of data elements that identify subjects with any link destroyed); coded (using numerical or other codes instead of names); or directly

¹ In the context of research, authors have suggested some useful definitions of privacy, including the following description from the National Bioethics Advisory Commission publication *Ethical and Policy Issues in Research Involving Human Participants*: “Privacy refers to persons and to their interests in controlling access of others to themselves [Boruch and Cecil 1979]. Confidentiality usually refers to data protection and those agreements and techniques that restrict disclosures of identifiable information about individuals.”

² Legal and regulatory protections for privacy and confidentiality necessary for the conduct of research are found in federal rules for human subjects protection (the Federal Policy for the Protection of Human Subjects, or the Common Rule (56 Federal Register 28002), and Food and Drug Administration regulations at 21 CFR Part 50 and Part 56), the new federal health privacy rule (the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 [HIPAA]), and state laws.

linked/identified. Investigators sometimes but not often require the names of subjects for research that uses existing data, but other identifying information may be important for the proposed analysis.

Data are identifiable when the data elements have personal information that can be linked to subject identity and/or other characteristics that (alone or in combination) could allow the person (research subject) to be identified. Potential identifiers include names, birth dates, dates of admission and discharge, dates of diagnosis, zip codes, identifying numbers (hospital, pathology record, Social Security), demographic details, and diagnosis. In addition, certain populations might be more readily identifiable, for example, those that are geographically isolated or certain groups or individuals such as those under study in rare disease research.

Identifiability of Coded Information. Because the Common Rule states that information is identifiable if the identity of the subjects could be “readily ascertained,” the question often arises whether the use of numerical codes instead of the names of subjects renders research exempt from the federal regulations.

When an investigator obtains private information about living individuals for research purposes and the private information retains a link to individually identifying information, the private information ordinarily would be considered individually identifiable to the investigator even when codes are used in lieu of subjects’ names or other identifiers. According to the Common Rule, Institutional Review Board (IRB) review and approval is required for such research, unless it meets one of the exemptions stated at §___46.101(b). The jurisdiction of the Food and Drug Administration (FDA) to regulate human subjects research does not depend on this standard of collection of identifiable information. Therefore, FDA regulations apply regardless of whether the data are identifiable if the activity otherwise falls within the definition of research found in 21 CFR 56.101 and 21 CFR 56.102.

According to the Office for Human Research Protections (OHRP), research that retains a link to identifying information ordinarily would not be considered human subjects research if, for example, the investigator and research institution do not have access to identifiable private information and a written agreement is obtained from the holder of the identifiable private information that such information would not be released to the investigator under any circumstances. In this

case, the research may be characterized as not involving human subjects, because the identity of the subjects could not be “readily ascertained” by the investigator and an institution or an IRB could determine that IRB review of the research is not needed. A determination that a research activity does not involve human subjects due to the use of coded information as described above is not the same as an activity that is deemed to be human subjects research and exempt from the regulations due to the application of one of the subsections of §___101(b).

Note that in order for research using coded data/biologic samples to be deemed not human subjects research, the samples or data for the specific research may not be obtained through an interaction or intervention with living individuals. Furthermore, those performing the coding of the data or samples and those holding the codes may not be part of the research team.³

OHRP Guidance on Screening Individuals as Potential Research Subjects. OHRP’s interpretation of Department of Health and Human Services (DHHS) regulations requires IRBs to review and approve research activities when an investigator obtains and records individually identifiable health information (i.e., identifiable private information), even when the information is used to identify individuals as potential participants in research. These screening activities are deemed human subjects research as defined under the Common Rule and would not satisfy the criteria for exemption under §___46.101(b). However, OHRP has stated that it expects that IRBs routinely will waive informed consent for activities involving the identification of subjects to be screened or recruited for a clinical trial. Moreover, in assessing the level of risk, the IRB need consider only the risk to subjects of investigators accessing their medical records, not the risks of the research in toto. As with other waivers of the requirement for informed consent under the Common Rule at §___116(d), IRBs must find and document that the research meets the waiver requirements listed previously.

Evaluating the Risk of Harm to Subject Privacy and Confidentiality

The sensitivity of the data may be assessed by examining the nature of the research, whether a particular stigma is attached to the disease or condition under study, whether the disease or condition is hereditary, whether there could be an impact on family members from learning of the research data or the facts of participation in a study, or whether the information could be of interest to legal authorities. The

³ The Office for Human Research Protection’s (OHRP’s) interpretation of the regulations for research using coded data and biologic samples has been published as part of OHRP’s *Guidance for Investigators and Institutional Review Boards Regarding Research Involving Human Embryonic Stem Cells, Germ Cells and Stem Cell-Derived Test Articles*, available at www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf. Also see www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm and <http://privacyruleandresearch.nih.gov/>.

researcher and the IRB share the responsibility of assessing the sensitivity of the data. To assess whether special privacy protections are necessary for a population under study, a review is needed to determine whether subjects with rare conditions are involved, whether the population is readily identifiable, and/or whether the subject matter of the research will result in the potential for stigmatization or discrimination if results of the research are revealed inappropriately.

IRBs and researchers need to evaluate the measures proposed to secure identifying data at all stages of research—from the time information is collected through the completion of analyses and publication of results—and for as long as the data are stored. IRBs should evaluate whether the level of protection described in research protocols is commensurate with the degree of risk of harm associated with the type of data collected. Protocols should include information pertaining to subject privacy and data confidentiality in sufficient detail so that the measures proposed for compliance with human subjects regulations, medical privacy legislation, and other regulations and laws can be assessed. The level of detail required may vary depending on the size of the study, the identifiability of the subjects, and the nature of research. The IRB should not hesitate to use outside consultants if it does not have expertise or knowledge needed to evaluate the potential risks in a proposed study.

Evaluating existing protections may include the review of the systems employed to protect against disclosures of research data (e.g., mechanical safeguards and electronic data security systems); state and federal statutory protections for privacy and health information; and the policies used to protect against disclosures, including operating policies employed to maintain data integrity, data storage and security, and institutional policies for the oversight of the collection, storage, and use of health information.

Methods of Protecting Subject Privacy and Confidentiality of Data

Protocol Design. Methods commonly employed to protect the confidentiality of research data include the use of codes, honest brokers, encryption methods, and data transfer restrictions. Other mechanisms to protect data include using locked storage files or rooms, limiting access on the part of members of the institution's staff, and keeping paper files at particular sites. The use of restricted laptop computers also should be considered, as well as whether computers that store data have links to the Internet or are closed terminals.

All links to subject identities should be evaluated by the IRB. This evaluation should include determining whether

codes are employed, who holds the link to identities (if retained), and methods of data storage and protection. When data that identify research subjects are no longer needed, the research records may be de-identified to further protect subjects.

Finally, in some research studies the necessity to preserve confidentiality does not exist. If identifiers are not recorded, there may be no need to protect confidentiality. In other cases, collecting identifiable information may be a necessary part of the research inquiry.

Informing Subjects About Privacy and Confidentiality.

During the informed consent process, subjects should receive information about confidentiality issues, including who will have access to the research data and for how long; what further disclosure or data sharing is anticipated; what data security measures will be employed; and what, if anything, will be disclosed to others, by whom, and under what conditions. Subjects also should be advised about whether study results will be made available to them; approximately when they will be available; and whether they can opt to know or not know the results and under what circumstances.

Subjects must be informed about researchers' obligations to protect subjects' privacy and confidentiality and about potential risks of harm if breaches should occur. Some research studies pose special risks to privacy, because of the sensitivity of the information gathered or the identifiability of the subject. Methods of protecting information vary by investigator and institution and according to the type of information and the identifiers used. In some cases, laws or rules may require investigators, physicians, or others to report identifiable information to state officials, public health authorities, or regulators. Healthcare providers or others (including researchers, if treatment is part of the study) may be required to report child abuse, elder abuse (in some states), and potential dangers to subjects or others. In cases where reporting is required, investigators must explain the circumstances to subjects and should present a notification plan to the IRB for review.

Subjects need to be informed whether they will receive findings of "significant" clinical concern (e.g., untreated medical problems) and if and when they will be contacted or recontacted by investigators. Subjects should also be informed regarding whether they will be asked to provide information about family members and if so what type of identifying information may be requested. Under certain circumstances, it may be appropriate to obtain the name of an individual who could receive information in lieu of contacting the subject directly. An individual who has not consented to enroll in a study (a third party) may be considered a human subject in the rare case that a subject has provided a

sufficient amount of identifiable information to render the third party a human subject and thus eligible for protection according to federal rules (see also Chapter 17).

Finally, when entering research studies of hereditary diseases or conditions, subjects should be advised that research results are not the same as validated clinical data, and they should be counseled accordingly.

Institutional Responsibilities. The role of the research institution is central to the safe and appropriate conduct of all research activities. The institution plays a critical role in ensuring the confidentiality safeguards stipulated by its investigators and IRBs. Specifically, investigators and IRBs are responsible for ensuring, implementing, and evaluating the efficacy of data protection plans, and institutions are responsible for supporting those plans and their mechanisms for evaluation in a manner that is consistent with existing legal protections. Research institutions should recognize and fulfill their obligations to actively support investigators in protecting all confidential information from compelled disclosure or as otherwise agreed on in the data protection plan.

Institutional policies are critical to protecting research data and subject privacy. These policies should be sufficiently flexible to account for the type of research, the range of research undertaken at the institution, and the technical protections available to investigators.

Identifiable research information can be protected through the development and implementation of institutional policies and standards, the development of education programs informing research personnel about appropriate uses of information, and the use of physical safeguards as well as protections for electronic data systems. The degree of access to data by researchers and other entities should be considered, including the proximity of research to data systems and the relationship of the investigator to the holders of the subject data. Other measures to preserve confidentiality and privacy include developing policies that restrict access to information to those who need it.

C. Federal Regulation of Privacy and Confidentiality

Federal Regulations Protecting Human Research Subjects

The Common Rule defines a human subject as a living individual about whom an investigator obtains “identifiable private information” (or alternatively, “data through intervention or interaction with the individual”). According to FDA, a subject is a human who participates in an investigation, either as an individual or whose specimen an investigational device is used or as a control. A subject may be in normal

health or may have a medical condition or disease (21 CFR §812.3(p)).

Because the characterization of an activity such as human subjects research often depends on whether identifiable private information is obtained, the determination of whether data are identifiable private information is a critical first step in deciding whether a research activity involves human subjects and the federal regulations apply. FDA regulations do not contain a parallel provision using the standard of “identifiable private information” in the definition of human subject at 21 CFR 56.102. However, the provision in the FDA regulations for IRB review of research, including a mandate to review measures to protect privacy and confidentiality, is identical.

The Common Rule provides further explication of what renders information private. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. It also includes information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record). The Common Rule states that private information must be *individually identifiable* for its study to constitute research involving human subjects. Information is considered individually identifiable when the identity of the subject is or may readily be ascertained by the investigator or associated with the information (45 CFR Part 46.102(f)).

FDA regulations at Title 21 CFR Parts 50, 56, and 812 do not address or define individually identifiable health information. However, 21 CFR §50.50.25(a)(5) requires, in seeking informed consent, that the subject must be provided with “a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.” 21 CFR §56.111(a)(7) directs the IRB to determine that, “where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.”

Federal regulations (§____.111(a)(7); 21 CFR 56.11(a)(7)) impose identical requirements that IRBs assess whether investigators propose to maintain adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data, where appropriate. Federal regulations also require that investigators include in the informed consent document a statement describing how the confidentiality of records identifying the subject will be maintained.

FDA and DHHS simultaneously published identical lists of categories of research that may be reviewed by the IRB through an expedited review procedure. An IRB may use the

expedited review procedure to review either or both of the following:

1. Some or all of the research appearing on FDA's and DHHS's expedited review list and found by the reviewers to involve no more than minimal risk
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized (21 CFR §56.110)

OHRP's *Guidance on the Use of Expedited Procedures* (2003)⁴ describes the categories of research that may be reviewed by an IRB using an expedited procedure. OHRP notes that research is ineligible for review by expedited procedure where "...identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal" (*emphasis added*).

Human subjects research may be exempt from the requirements of the Common Rule if the activity falls within any of six categories of research established in the federal rules, which are addressed elsewhere in this publication. Three of the exempt categories depend on identifiability of subjects. Exemption (b)(2) for research involving the use of some educational tests⁵ requires that the exemptions for educational tests and research involving existing data depend on the determination of whether the research data are recorded by the investigator "in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects" (§___101(b)(2) and (3)).

Exemption (b)(4) for research involving existing data⁶ and exemption (b)(5) for research and demonstration projects on public benefit and service programs require meeting the criterion that the project does not involve "significant physical invasions or intrusions upon the privacy of participants."

OHRP Guidance on Exemption from Human Subjects Regulations for "Existing Data"

According to 45 CFR Part 46.101(b)(4), research activities that involve the use of existing data, documents, records, pathological specimens, or diagnostic specimens are exempt from DHHS regulations covering human subjects research under the following circumstances:

- The information exists at the time the research is proposed
- Either
 - the information recorded is not directly or indirectly identifiable (i.e., coded information is deemed indirectly identifiable unless other protections exist as described in the previous section) or
 - the information is publicly available.⁷

OHRP interprets the phrase "existing data or specimens" to mean those that are stored or "on the shelf" or "in the freezer" at the time the research begins (OPRR 1993).

When research uses existing data or records for social sciences research, OHRP has stated that, if the records were filed before the research was initiated, the protocol would qualify as exempt under 46.101(b)(4). If the research uses records filed after the initiation of the project, the protocol is not exempt from IRB review, although it may qualify for expedited review.⁸

⁴ See www.hhs.gov/ohrp/humansubjects/guidance/exprev.htm.

⁵ 45 CFR Part 46.101(b)(2) describes research "involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation" (*emphasis added*).

⁶ 45 CFR Part 46.101(b) describes research "As discussed elsewhere in this volume, the federal regulations establish categories of exempt research for certain types of activities involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects" (*emphasis added*).

⁷ Research that involves obtaining specimens or information from repositories that can be conducted without obtaining identifiable information would not be deemed human subjects research under the definition of human subjects research in 45 CFR Part 46.102.

⁸ For further information see www.hhs.gov/ohrp/humansubjects/guidance/hssc95-02.htm.

OHRP Guidance on Exemption from Human Subjects Regulations for Public Benefit and Service Programs

OHRP guidance⁹ describes the criteria that must be satisfied for research to be deemed exempt under 45 CFR Part 46.101(b)(5).

OHRP sets out four elements that must be met for exemption of Research and Demonstration Projects on Public Benefit and Service Programs, as follows:

1. The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
2. The research or demonstration project must be conducted pursuant to specific federal statutory authority.
3. There must be no statutory requirement that an IRB review the project.
4. *The project must not involve significant physical invasions or intrusions upon the privacy of participants* (emphasis added).

Upon the application of a sponsor or sponsor-investigator, FDA may waive any of the requirements contained in Part 56, including the requirement of IRB review, for specific research activities or for classes of research activities otherwise covered by Part 56 (see 21 CFR §§56.104 and 56.105). However, §520(g)(3)(A) of the act requires meaningful IRB review and approval; thus, complete waiver of IRB review and approval is not permitted for device studies.

Health Information Privacy and the Conduct of Human Subjects Research

The Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (PL 104-191, 110 Stat. 1936) imposes stringent conditions on the uses and disclosures of protected health information. Research that uses health information may be subject to HIPAA if the information is identifiable, is obtained from a covered entity, or is used or disclosed by a covered entity (although not all institutions conducting research are covered entities). Institutions should consult the DHHS Office for Civil Rights to obtain further information regarding their status as covered entities, hybrid entities, or business associates under this rule.¹⁰ HIPAA does not replace or alter federal requirements for the conduct of human subjects research. However, for research involving the use or disclosure of health information, HIPAA imposes several new and significant requirements regarding authorization for such uses. For the conduct of research, IRBs and investigators should be aware of the

differing terms and how they affect subjects' privacy and confidentiality.

The HIPAA Privacy Rule specifies 18 data elements that alone or combined render data individually identifiable and subject to restrictions on uses and disclosures when used or held by covered entities. Health information that is fully de-identified (the 18 data elements are removed or statistical certification that no re-identification is possible is obtained) is not covered by HIPAA.

For example, a covered entity may determine that health information is de-identified even if the health information retains a code or other means of record identification. To do so requires that the code not be derived from or related to the information about the individual, that the code could not be translated by the investigator to identify the individual, and that the covered entity does not use or disclose the code for other purposes or disclose the mechanism for re-identification.

HIPAA requires that written patient authorization be obtained when protected health information is used or disclosed (unless a waiver of authorization is obtained or another exception exists). This requirement is in addition to the existing rules for obtaining informed consent from research subjects. Neither the scope nor content of a HIPAA authorization is the same as an informed consent document as required under federal regulations. A HIPAA authorization

⁹ See www.hhs.gov/ohrp/humansubjects/guidance/exmpt-pb.htm. Commentary published in the *Federal Register* describes the intended application of this exemption to research on proposed or potential changes in levels of benefits or services or in their delivery to recipients of federal statutory entitlements. The comments indicate that the justification for this exemption derived from the DHHS belief that to require IRB review and approval (as provided by 45 CFR Part 46) would be "duplicative and needlessly burdensome in light of the substantial review process to which [these research projects] are already subject by state and federal offices." The comment also states that additional IRB review that focuses on ethical questions arising from biomedical and behavioral research may be unnecessary and inappropriate in the context of making adjustments to benefit and service programs.

¹⁰ The reader is encouraged to regularly check the Web site of the Office for Civil Rights for updates on HIPAA at www.hhs.gov/ocr/hipaa/.

must satisfy stringent criteria. Most importantly, an authorization is limited to a specific use or disclosure.

Exceptions apply to the requirement for written authorization for research uses or disclosures when research is on a decedent's information or the use of protected health information is preparatory to research, used solely to prepare a protocol, not removed from the covered entity, and deemed necessary for research.

Preparatory to Research. HIPAA permits a covered entity to allow investigators to access protected health information in the covered entity's medical records for certain activities that are preparatory to research. Activities that are preparatory to research are those undertaken for the purpose of identifying potential human subjects to aid in the preparation of a protocol or to determine the feasibility of conducting a study. (When conducting activities that are preparatory to research, one may not remove protected health information from the covered entity.)

Limited Datasets and Research. The Privacy Rule permits a covered entity to use and disclose protected health information for research without obtaining patient authorization the information is part of a limited dataset. A limited dataset is described as health information that excludes certain listed direct identifiers but that may include city, state, zip code, elements of date, and other numbers, characteristics, or codes not listed as direct identifiers. The direct identifiers listed in the Privacy Rule limited dataset provisions apply both to information about the individual and to information about the individual's relatives, employers, or household members. The following identifiers must be removed from health information if the data are to qualify as a limited dataset:

- names
- postal address information, other than town or city, state, and zip code
- telephone numbers
- fax numbers
- electronic mail addresses
- social Security numbers
- medical record numbers
- health plans beneficiary numbers
- account numbers
- certificate/license numbers
- vehicle identifiers and serial numbers, including license plate numbers
- device identifiers and serial numbers
- web universal resource locators (URLs)
- internet protocol (IP) address numbers
- biometric identifiers, including fingerprints and voiceprints
- full-face photographic images and any comparable images

Limited datasets may be used or disclosed only for the purposes of research, public health, or healthcare operations. Because limited datasets may contain identifiable information, their use is still considered a use of protected health information.

Covered entities must use a data use agreement to obtain satisfactory assurances that the recipient of the limited dataset will use or disclose the protected health information in the dataset only for specified purposes. Even if the person requesting a limited dataset from a covered entity is an employee or otherwise a member of the covered entity's workforce, a written data use agreement meeting the Privacy Rule's requirements must be in place between the covered entity and the limited dataset recipient.

The data use agreement must establish the permitted uses and disclosures of the limited dataset by the recipient, consistent with the purposes of the research. It may not include any use or disclosure that would violate the Privacy Rule if done by the covered entity; it must limit who can use or receive the data; and it must require the recipient to agree to the following:

- not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law
- to use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement
- to report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware
- to ensure that any agents, including a subcontractor, to whom the recipient provides the limited dataset agrees to the same restrictions and conditions that apply to the recipient with respect to the limited dataset
- not to identify the information or contact the individual

HIPAA and Multisite Research. IRBs may consider and act on requests for a partial or complete waiver or alteration of the Privacy Rule's authorization requirement for uses and disclosures of protected health information for research. Provisions concerning requests to an IRB for a waiver or an alteration of the authorization requirement are found in section 164.512(i) of the Privacy Rule. An IRB approval for a waiver or an alteration of authorization may be issued by an IRB that is unrelated to the institution conducting or sponsoring the specific research project, unrelated to the covered entity that creates or maintains the protected health information to be used or disclosed for research, or different from the IRB with responsibility for monitoring the underlying research project. As a result, a waiver or an alteration of the Privacy Rule's authorization requirements could be obtained from a

single IRB in connection with a multisite research activity or where the protected health information necessary for the research is to be used or disclosed by more than one covered entity.

Patient Authorizations and Informed Consent. Under the Privacy Rule, an authorization may be combined with the informed consent document for research. If the informed consent document is combined with an authorization meeting the Privacy Rule's requirements, the Common Rule and FDA regulations would require IRB review of the combined document.

An IRB's role under the Privacy Rule is limited to acting on requests for a waiver or an alteration of the Privacy Rule's authorization requirement. IRBs are not required to review and approve authorizations under the Privacy Rule. Likewise, IRBs are not required to approve stand-alone authorizations (i.e., authorizations that are not incorporated into the informed consent document) under the Common Rule or FDA regulations. However, FDA regulations could require such review if required by the IRB's written procedures. In the exercise of ongoing enforcement discretion, however, with respect to the requirements of 21 CFR 56.108(a), to the extent that an IRB's written procedures require the review and/or approval of stand-alone authorizations, FDA will not take enforcement action against an IRB for failing to review them even when the IRB's written procedures otherwise would require such review and/or approval.¹¹

Criteria for Waiver or Alteration of Authorization

The Privacy Rule establishes the criteria to be evaluated by an IRB in approving an authorization waiver or alteration. Furthermore, the criteria for an IRB waiver or alteration of the authorization in whole, or in part, differ from the criteria for IRB waiver of the informed consent requirements contained in the Common Rule. In order for a covered entity to use or disclose protected health information under a waiver or an alteration of the authorization requirement, it must receive documentation of, among other things, the IRB or Privacy Board's determination that the following criteria have been met:

- The protected health information use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of an adequate plan presented to the IRB to protect protected health information identifiers from improper use and disclosure; an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is

otherwise required by law; and adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the protected health information is permitted by the Privacy Rule.

- The research could not practicably be conducted without the requested waiver or alteration.
- The research could not practicably be conducted without access to and use of the protected health information.

Privacy Boards. Before a covered entity can use or disclose protected health information for research under a waiver or an alteration of authorization, it must obtain documentation of approval of the waiver or an alteration of the authorization requirement by either a Privacy Board or an IRB. As an alternative to IRB review of requests for waiver or alteration of authorization, a covered entity may establish a separate Privacy Board to accomplish these reviews. The Privacy Board acts solely on requests for a waiver or an alteration of the authorization requirement under the Privacy Rule for uses and disclosures of protected health information for a particular research study. A Privacy Board can waive or alter all or part of the authorization requirements for a specified research project or protocol.

Privacy Boards, however, do not exercise any of the other powers or authority granted to IRBs under federal laws relating to federally conducted or supported human subjects research and research involving products regulated by FDA. Under the Privacy Rule, Privacy Boards are not involved in creating authorization forms and do not monitor the uses and disclosures of protected health information made pursuant to an authorization. A Privacy Board that meets the membership requirements of the Privacy Rule does not necessarily satisfy the IRB membership requirements of the DHHS or FDA regulations or the requirements of other federal laws applicable to the related research.¹²

Summary of Additional Federal Privacy and Confidentiality Statutes

In addition to the major federal regulatory requirements described above, other federal statutes may have relevance to some types of research in which subject records are in the possession of the federal government. These are briefly described below.

Privacy Act of 1974. The Privacy Act of 1974¹³ prohibits disclosures of an individual's federal government records to

¹¹ See Office for Civil Rights guidance at www.hhs.gov/ocr/hipaa/privguideresearch.pdf for more information.

¹² To view the complete final Privacy Rule see www.hhs.gov/ocr/hipaa/finalreg.html.

¹³ 5 USC 552(a).

any person or other agency without prior written consent and provides access to review, copy, and correct records. The Privacy Act covers personally identifiable data held by the federal government, no matter what their source or subject, that are stored in “systems of records” from which data are retrieved by the agency using personal identifiers. It covers regulatory data held by FDA, statistical data held by the National Center for Health Statistics, and public health surveillance data held by the Centers for Disease Control and Prevention.

However, under the Privacy Act, federal agencies are allowed wide discretion in making disclosures pursuant to their mandates. They may designate information as being eligible for routine use disclosures without the consent of the subjects if the data are “for a purpose which is compatible with the purpose for which it was collected.” Routine uses must be announced in the *Federal Register*, and the conditions on use are restrictive. Furthermore, because the act applies only to federally operated hospitals and to research or health-care institutions operated pursuant to federal contracts, it does not cover the vast majority of organizations and entities collecting health-care information. In addition, disclosure of personally identifiable information is permitted broadly for the routine use of the receiving facility.

The Privacy Act does not negate the provisions of the Freedom of Information Act (FOIA) (5 USC 552) (the law that provides transparency in federal records by allowing citizens access to them), because exemption 6 of FOIA states that it does not apply to “personal and medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.”

Freedom of Information Act. FOIA requires that public agencies make available to the public copies of records, agency rules, opinions, orders, and proceedings. FOIA exempts from its requirements information such as medical or personnel records, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

The Controlled Substances Act (21 USC 872).¹⁴ The Department of Justice (DOJ) permits the U.S. Attorney General to authorize persons conducting educational or research programs concerning drug abuse to withhold the names and other identifying characteristics of the subjects of such research. This provision is implemented by FDA regulations published at 21 CFR 1315.21.

D. State Regulation of Privacy and Confidentiality

Researchers and IRBs should be aware that state laws may impose additional restrictions beyond the Common Rule or FDA regulations. Various state laws limit the release of health information, restrict the uses of genetic information, or confer additional protections for human subjects. Local laws must be complied with in addition to the federal regulations, because both FDA and the Common Rule do not affect any state or local laws or regulations that may otherwise be applicable and that provide additional protections for human subjects.

Virtually every state addresses the confidentiality of health records, privacy, and/or health information in some manner. Some state statutes require that medical records or health information be maintained in a confidential manner, while others have enacted general privacy statutes that extend beyond health information, and still others restrict the acquisition, retention, and use of genetic information. In some jurisdictions, substance abuse or mental health treatment records or AIDS/HIV counseling and treatment records may not be disclosed to unauthorized persons, while other states require disclosures, such as mandatory reporting of child abuse, the provision of information for newborn screening programs, or reporting to public health and epidemiological registries.

Most states have passed laws that limit the disclosure and use of medical information. Some states permit the disclosure of medical information for research purposes under certain conditions without the informed consent of individuals. Examples of some of the conditions under which the release of information is permitted include allowing disclosures for research when the subject identities are not disclosed, when the data are anonymous, when an IRB approves, or when research is conducted pursuant to federal regulations.

More than half of the states restrict the use of genetic information or information derived from genetic tests. These statutes usually limit the use of information derived from clinical or diagnostic genetic tests and are intended to prohibit discrimination in the provision of insurance or employment. Certain state statutes specifically address the use of genetic information for research purposes. Often, these statutes permit the use of genetic information for

¹⁴ Identification of research populations; authorization to withhold. The Attorney General may authorize persons engaged in research to withhold the names and other identifying characteristics of persons who are subjects of such research. Persons who obtain this authorization may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding to identify the subjects of research for which such authorization was obtained.

research purposes when the identity of the individual is not disclosed or under conditions similar to those provided for under state statutes that allow the release of medical information for research (see above).

State laws fulfill a variety of functions, all of which require information disclosures, including:

- the regulation of health insurance;
- the regulation of organizations that perform certain administrative functions such as utilization review or third-party administration;
- licensure requirements for various medical specialties and medical organizations (including requirements for record keeping and disclosure);
- access to medical records by patients, guardians, and other interested parties;
- the use of information for quality assurance and health care operations;
- issuance of notices of privacy practices; and
- reporting and providing access to law enforcement authorities.¹⁵

Public Health Surveillance and Research: State Disease Registries

Many states monitor the health of their citizens and conduct research on the spread and etiology of disease through the creation of hospital-based and population-based databases and registries for both chronic and communicable diseases. When reviewing research involving the use of health information contained in state databases, special state law privacy and confidentiality rules often apply. Statutes authorizing states to collect disease information also often include prohibitions against unauthorized release. However, some statutes permit the release of information for research purposes when the identities of subjects are not disclosed or with IRB approval of the research.

State Newborn Screening Programs

Newborn screening programs are a type of public health

surveillance that involves testing for certain diseases and the creation of databases that track newborn health information using blood specimens collected during a newborn's first few days of life. Currently, all states require newborn screening, and state newborn screening statutes usually do not require parental consent.¹⁶ Provisions regarding the confidentiality of screening results are included in state newborn screening statutes and regulations and state genetic privacy laws, but they are often subject to exceptions, which vary across states.

In the majority of states, newborn screening statutes and regulations have provisions that indicate that the information collected from the screening is confidential. In some circumstances, these statutes permit information to be released without authorization from the child's legal representative. The most common provision for the release of screening information is for use in statistical analysis or research, generally with a requirement that the identity of the subject is not revealed and/or that the researchers comply with applicable state and federal laws for the protection of humans in research activities. Some state screening statutes have additional provisions that allow screening information to be released.¹⁷ The most common exceptions, besides disclosure of information for research purposes, are for use in law enforcement and for establishing paternity. Few newborn screening statutes provide penalties for the violation of confidentiality provisions.

State Genetic Privacy Laws

Many states have statutes that govern the collection, use, and disclosure of genetic information. Twenty-five states have laws that prohibit the disclosure of genetic information without the consent of the individual; in 23 of these states, the statutes have exceptions that permit disclosure without consent.¹⁸ For example, 14 state genetic privacy laws permit the disclosure of genetic information without consent for the purpose of research, provided that the identities of individuals are not revealed and/or the research complies with applicable state and federal laws for the protection of humans in research activities.¹⁹ Some states have genetic privacy laws that relate to other issues, such as the prohibition against using genetic information to deny insurance or employment.

¹⁵ A comprehensive survey of all of the state laws affecting medical and health privacy is beyond the scope of this publication; however, further information may be found in *Compilation of State and Federal Privacy Laws* (Smith 2002); *50-State Survey on Patient Health Care Record Confidentiality* (American Health Lawyers Association 1999); *The State of Health Privacy: An Uneven Terrain* (Health Privacy 2002); and the "State Genetic Privacy Laws" table, National Conference of State Legislatures, at www.ncsl.org/programs/health/genetics/prt.htm.

¹⁶ See the National Conference of State Legislatures Report on Newborn Genetic Screening Privacy Laws (July 2002) at www.ncsl.org/programs/health/screeningprivacy.htm. The Government Accountability Office also has published a report, *Newborn Screening: Characteristics of State Programs* (March 2003).

¹⁷ Wisconsin's screening statute, for example, allows the information to be released for use by health care facilities staff and accreditation organizations for audit, evaluation, and accreditation activities and for billing, collection, or payment of claims. A few states have more restrictive provisions. South Carolina's screening statute, for example, limits disclosure of the information obtained from screening to the physician, the parents of the child, and the child when he/she reaches age 18.

¹⁸ Rhode Island and Washington require written authorization to disclose genetic information. Colorado, Florida, Georgia, and Louisiana explicitly define genetic information as personal property. In 2001 Oregon repealed its property right to DNA samples and genetic information. Seventeen states have established specific penalties—civil or criminal—for violating genetic privacy laws.

¹⁹ See www.ncsl.org/programs/health/screeningprivacy.htm.

HIPAA and State Privacy Protections

The HIPAA Privacy Rule does not preempt any state laws that relate to the privacy of individually identifiable health information or provide greater privacy protections or privacy rights with respect to such information; provide for the reporting of disease or injury, child abuse, birth, or death; provide for public health surveillance, investigation, or intervention; or require certain health plan reporting, such as for management or financial audits.²⁰ When states impose more stringent protections on the uses and disclosures of health information, these state requirements must be observed.

For example, the Privacy Rule permits covered health care providers and other covered entities to disclose reports of child abuse or neglect to public health authorities or other appropriate government authorities. Covered entities can report such information and be in compliance with both the state law and the Privacy Rule. Similarly, HIPAA permits compliance with state law, where the law requires reporting of disease or injury, child abuse, birth, or death or requires public health surveillance, investigation, or intervention—even when such reporting is otherwise contrary to a provision of the Privacy Rule.

E. Special Issues

Sensitive Research and Certificates of Confidentiality

The Public Health Service Act²¹ grants the Secretary of DHHS authority to allow persons engaged in sensitive research (biomedical, behavioral, clinical, or other) to protect the identity of individuals who are the research subjects. Sensitive research is that for which the disclosure of identifying information could have adverse consequences for subjects or by damaging their financial standing, employability, insurability, or reputation. Examples of sensitive research activities include but are not limited to the following:

- collecting hereditary information
- collecting information on the psychological well-being of subjects
- collecting information on subjects' sexual attitudes, preferences, or practices
- collecting data on substance abuse or other illegal risk behaviors

A Certificate of Confidentiality is a tool to prevent compelled disclosure of subject identities by investigators.

Neither voluntary disclosure by research subjects nor requests for disclosure by subjects are covered under this tool, and subjects may disclose information to physicians or third parties. Subjects also may authorize investigators to release the information to insurers, employers, or other third parties. In such cases, investigators may not use the certificate to refuse disclosure.

Investigators are not prevented from and indeed may have a duty to disclose matters such as child abuse, reportable communicable diseases, or threats of violence to subjects or others. Investigators cannot refuse to disclose information if disclosure is required by the Federal Food, Drug, and Cosmetic Act.

The consent form should specify whether investigators intend to make any voluntary disclosures. Further, investigators must tell research subjects that a certificate is in effect and provide a fair and clear explanation of the protection that it affords, including its limitations and exceptions. Every research project that includes human subjects should inform those subjects how identifiable information will be used or disclosed and whether or not a certificate of confidentiality is in effect.

The National Institutes of Health (NIH), FDA, and other federal agencies issue Certificates of Confidentiality to the institutions (research sites) where the research is conducted. OHRP does not issue Certificates of Confidentiality.²² Finally, Certificates of Confidentiality cannot replace clear and effective policies for data protection and security, which are essential to the protection of the privacy of research subjects.

Mental Health Research

There is no national standard for the confidentiality of mental health care information other than HIPAA. Many states have laws that establish confidentiality rules and exceptions. In certain states, mental health confidentiality statutes apply only to information gathered when treatment is provided by a state facility, while in others it applies to mental health treatment and not research specifically.

HIPAA defines identifiable mental health information as one of the elements of protected health information. However, HIPAA imposes special restrictions on the release of notes from psychotherapy. Under HIPAA, disclosure of psychotherapy notes requires individual patient authorization or specific permission. Although in the past insurance

²⁰ See 45 CFR Part 160, Subpart B, for specific requirements related to preemption of state law.

²¹ Section 301(d) of 42 USC 241(d). The legal authority of a Certificate to protect an investigator against compelled disclosure has rarely been tested. In 1973, the Certificate's authority was upheld in the New York Court of Appeals (*People v. Newman*) (32 N.Y.2d 379, 298 N.E.2d 651, 345 N.Y.2d 502, 1973). The U.S. Supreme Court declined to hear the case.

²² In 2002, the National Institutes of Health issued new guidance on the use of certificates of confidentiality. Information on these certificates can be found at <http://grants1.nih.gov/grants/policy/coc/>.

companies have requested entire patient records, including psychotherapy notes, for making coverage decisions, health plans now cannot refuse reimbursement if a patient does not agree to release information covered under the psychotherapy notes provision.²³

Records of Substance Abuse

Information related to substance abuse and chemical dependency treatment is protected by the Public Health Service Act. This regulation, which supersedes both HIPAA and all the more permissive state laws, requires that any disclosure of information related to substance abuse and chemical dependency treatment be accompanied by the individual's signed authorization. There are no exceptions for disclosures related to treatment, payment, or health-care operations. The only exception relates to movement of information between different components of the Armed Services, including the Department of Veterans Affairs. Although the regulation applies only to federally supported specialized alcohol or drug abuse programs, it is widely interpreted as applying to any federally conducted or funded program, any federally licensed or certified program, programs that are tax exempt, and programs that receive federal funds in any form, such as through the Medicaid program.

Because significant differences remain among states, and between the state and federal requirements, investigators conducting research in this area and IRBs reviewing research should check state laws before proceeding. Federally supported drug abuse programs are subject to the Confidentiality of Alcohol and Drug Abuse Patient Records regulation.^{24, 25}

Public Health Activities and Research

Public health practice often requires the acquisition, use, and exchange of health information. Most states, as well as the federal government, have laws that govern the use of, and serve to protect, identifiable information collected by public health authorities.²⁶

Most public health activities (e.g., public health surveillance, disease prevention and control projects, program evaluation, terrorism preparedness, outbreak investigations,

direct health services, and public health research) require data collection or analytic methods that are similar to those used in research (e.g., identifying, monitoring, and responding to death, disease, and disability among populations). However, they are not designed to contribute to generalizable knowledge and do not readily fit within the definition of research used in the federal regulations.

Entities that conduct public health research or that perform public health activities must protect the confidentiality of the data that are collected and stored for these purposes. When public health entities conduct research, or when activities that are initially public health practice evolve into research activities (e.g., an investigation to determine the cause of an outbreak that incorporates a research study evaluating the efficacy of a new drug to treat the illness), these entities are obliged to protect participant privacy in accordance with federal human subjects protection regulations and HIPAA.

With respect to compliance with HIPAA, the Privacy Rule permits covered entities to disclose protected health information to public health authorities when required by federal, tribal, state, or local laws (45 CFR 164.512(a)). This includes state laws (or state procedures established under state law) that provide for receiving reports of disease or injury, child abuse, birth, or death, or conducting public health surveillance, investigation, or intervention.

For disclosures not required by law, covered entities may still disclose, without authorization, to a public health entity authorized by law to collect or receive the information for the purpose of preventing or controlling disease, injury, or disability, the minimum necessary information to accomplish the intended public health purpose of the disclosure (45 CFR 164.512 (b)). The Privacy Rule continues to allow for the existing practice of sharing protected health information with public health authorities who are authorized by law to collect or receive such information.²⁷ Examples of such activities include those directed at reporting disease or injury, reporting adverse events, reporting births and deaths, and investigating the occurrence and cause of injury and disease.

For ongoing research activities that fall under HIPAA, the entity must follow the relevant research disclosure provisions to continue to obtain information. Moreover, cases may occur

²³ For further information see Chapter 7, "Confidentiality of Mental Health Information," in *Mental Health: A Report of the Surgeon General* (Public Health Service 1999), at www.surgeongeneral.gov/library/mentalhealth/home.html.

²⁴ Title 42 CFR Part 2 at www.access.gpo.gov/nara/cfr/waisidx_02/42cfr2_02.html.

²⁵ Educational materials on the relationship between the Privacy Rule and the Confidentiality of Alcohol and Drug Abuse Patient Records regulation as they relate to research are described on the SAMHSA Web site at www.hipaa.samhsa.gov/.

²⁶ Comprehensive DHHS guidance can be found at the Office for Civil Rights HIPAA Web site at www.hhs.gov/ocr/hipaa/.

²⁷ DHHS has interpreted the phrase "authorized by law" to mean that a legal basis exists for the activity. DHHS has determined that this phrase covers both actions that are permitted and actions that are required by law (64 *Federal Register* 59929, November 3, 1999).

where the activity is considered both research and public health practice (e.g., an ongoing survey to monitor health conditions, data from which also can be analyzed for research purposes). In such cases, disclosures may be made either under the research provisions or the public health provisions, as appropriate. The covered entity does not need to comply with both sets of requirements.²⁸

Health Services Research

Health services research is a multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, delivery, organization, financing, and outcomes of healthcare services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations.

Health services research frequently makes use of information that has already been collected for other purposes. In addition, as compared with clinical research, which is often prospective, health services research is generally retrospective and may involve the review and analysis of records from thousands of individuals collected for other purposes. Health services research risks are those associated with risks to subject privacy and data confidentiality through the inappropriate release of information rather than the physical risks associated with clinical or biomedical research. For example, often, through the process of creating and combining longitudinal records to develop records of cohorts of individuals who are followed over time, encrypted numbers or sequences replace personal identifiers, but these data are not fully anonymous as long as someone holds the key or the link to the individual identities. This can happen with epidemiological research, because links to

patient identifiers (study site identifiers or patient sequence numbers) often are retained for data analyses, and investigators or institutions usually retain the links between these “codes” or numbers and patient identifiers. IRBs should consider the risks that research presents if information is disclosed inappropriately.

Students and Educational Records

Federal privacy laws²⁹ apply to educational agencies, institutions, and schools that receive federal funds from the U.S. Department of Education. The Family Educational Rights and Privacy Act, which protects most information collected by schools about students,³⁰ is designed to protect student records from disclosure without consent from parents or from students over 18 years of age. The Protection of Pupil Rights Amendment gives parents the right to review their child’s records.³¹ Other federal laws, such as the Individuals with Disabilities Education Act, address data collection, maintenance, and disclosure procedures for students in special education programs.³²

Children/Minors

The federal regulations for human subjects protection do not establish specific privacy protections for children who are research subjects, and HIPAA does not protect children’s health information differently from that of adults, although there are special provisions for access to a minor’s health records under HIPAA. The Privacy Rule generally allows a parent access to his/her child’s medical records when such access is not inconsistent with state law.³³

²⁸ For more information, see also Snider and Stroup (1997); Centers for Disease Control and Prevention *Guidelines for Defining Public Health Research and Public Health Non-Research* at <http://www.cdc.gov/od/science/regs/hrpp/researchDefinition.htm>; Amoroso and Middaugh (2003); and *Public Welfare: Protection of Human Subjects* (OHRP 2001), available at www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

²⁹ The Buckley Amendment to the General Education Provisions Act (20 USC 1232) requires parental permission for access to records or identifiable information of children in public schools.

³⁰ Teachers’ informal notes, records of school-based law enforcement units, and employment records do not fall under the jurisdiction of this law. Directory information of individual students may be released without prior consent.

³¹ The Protection of Pupil Rights Amendment (PPRA) gives parents the right to consent for their children to participate in sensitive research. The PPRA applies to programs that receive funding from the U.S. Department of Education. This law requires that schools and contractors obtain written consent from the parents before minor students are required to participate in a survey, analysis, or evaluation that reveals certain information. The PPRA requires education agencies to establish procedures for parents to follow if they believe their rights are violated under PPRA.

³² The privacy of special education records is protected by the Family Educational Rights and Privacy Act and by the Individuals with Disabilities Education Act. Any participating agency or institution that collects, maintains, or uses personally identifiable information about students with disabilities must protect the privacy of these special education records. Records pertaining to the identification, evaluation, and educational placement of children with disabilities must be available for inspection by parents. Agencies must maintain, for public inspection, a list of employees who have access to personally identifiable information. State and local education agencies must designate a person who is trained in privacy protection policies and procedures to serve as the custodian of the special education records of children with disabilities.

³³ There are three situations when the parent would not be the minor’s personal representative under the Privacy Rule: (1) when the minor is the one who consents to care and the consent of the parent is not required under state or other applicable law; (2) when the minor obtains care at the direction of a court or a person appointed by the court; and (3) when, and to the extent that, the parent agrees that the minor and the healthcare provider may have a confidential relationship. However, even in these exceptional situations, the parent may have access to the medical records of the minor related to this treatment when state or other applicable law requires or permits such parental access.

However, federal regulations establish certain conditions under which parental permission may be waived. This waiver is sometimes used to protect the privacy and confidentiality of child subjects and the confidentiality of their information (for example, research involving child abuse). For research sponsored or conducted by DHHS, 45 CFR 46, Subpart D, "Additional DHHS Protections for Children Involved as Research Subjects," permits IRBs to waive the requirement to obtain the consent of parents if the IRB determines that a research protocol is designed for a subject population for which "parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children)." Accordingly, IRBs may waive parental permission only if an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. According to the regulations, "the choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition" (45 CFR 46.408 (c)).

When children are involved as research subjects, they must be informed that sensitive information will be collected about them (for example, drug abuse information, positive pregnancy tests), and they must be told whether the information will be reported to their parents. Parents must be advised whether they will receive the results of questions about their children.³⁴

Prisoners

DOJ has drafted regulatory protections for prisoners (28 CFR Part 512), giving them control over their data, requiring at least one prisoner and a majority who are not prison personnel to be members of the IRB reviewing the research and prohibiting prison administrators from accessing research data.

OHRP released new guidance on the involvement of prisoners in research in May 2003. The document describes the requirements of the DHHS regulations at 45 CFR, Subpart C, which provide additional protections to prisoners involved as subjects in biomedical and behavioral research conducted or supported by DHHS.

Although the guidance does not impose specific privacy requirements for the conduct of research involving prisoners, protecting the privacy of prisoners who participate in research, or even those who are approached as potential participants, poses a special challenge. Simply identifying

certain prisoners as eligible to participate in a trial may compromise their privacy and expose them to risk. Protecting the privacy of prisoners is challenging even when they are not part of a study. For example, being moved from a cell to a clinic can make an inmate conspicuous to others. Because nonmedical staff may have access to medical records, maintaining confidentiality for inmates might require elaborate safeguards and protections, including storing study-related documents separately from the medical records, integrating study visits with routine clinic visits, and carefully labelling any medication dispensed.

Genetics Research

Research into hereditary conditions often involves complex concepts of risks and percentages and the evaluation of complex interactions with environmental and other exposures. From the standpoint of protecting individual privacy and the confidentiality of data, investigators should be aware of several important legal and regulatory issues. HIPAA considers genetic information protected health information under the Privacy Rule and does not provide different protections for genetic information. (See Chapter 24 for a thorough treatment of issues involving genetic research.)

State laws sometimes protect against unauthorized disclosures and uses of genetic information. More than half of the states have enacted special legislation imposing limits on clinical genetic tests and the acquisition of genetic information. The types of restrictions imposed include requiring individual permission to perform a genetic test, collect genetic information, or retain genetic information. Other states restrict disclosures of genetic information, especially to insurers or employers, and prohibit the use of genetic information in the provision of insurance or employment.

Classified Research

Classified research often involves an abridgement of the requirements of open inspection, appraisal, and publication. Research may be classified with respect to its primary sources, the process itself, or its product, and the abridgement or classification can be made in the interest of the government, corporate organizations, or individuals.

Classified projects are not published in the open literature. Information is transferred only to those who have the required security clearance, which applies even when scientists outside of government facilities perform the research. Many universities do not accept classified projects,

³⁴ In certain circumstance, parents may agree not to request access to certain information about their children, but this is not binding generally.

and many of those that do accept them conduct research in facilities separate from the main campus.

DHHS regulations do not distinguish between classified and unclassified research in terms of the requirements or procedures they impose to protect human subjects; however, according to OHRP regulations, the expedited review procedure cannot be used for classified research involving human subjects.

Executive Order 12958, issued on April 17, 1995, prescribes a uniform system for classifying, safeguarding, and declassifying national security information.³⁵

Third Parties in Research

In the course of participating in a research study, a human subject may provide information to investigators about other persons, such as a spouse, relative, friend, or social acquaintance (third parties). In recent years, questions have arisen in the research community about whether the Common Rule applies to third parties in research and

whether third parties are human subjects or whether they can become human subjects during the course of research. The Common Rule does not specifically address third-party information, and the definition of human subject leaves some room for interpretation in this regard.

Under certain circumstances, investigators and IRBs may need to consider whether third parties are entitled to some protection of their privacy interests. This issue has been the subject of recommendations by NIH,³⁶ OHRP, and the National Human Research Protections Advisory Committee (the predecessor of the Secretary's Advisory Committee for Human Research Protections convened by the DHHS Secretary). Although no clear consensus has emerged, third parties are not usually considered human subjects (or entitled to statutory or regulatory privacy protections), unless the nature and scope of the information gathered, combined with the inability of investigators to maintain the confidentiality of that data, makes it necessary to consider them to be human subjects in a particular research project according to the regulatory definition.

³⁵ Unclassified Information: The Computer Security Act of 1987 (PL 100-235) established requirements for the protection of certain information on federal government automated information systems. This information is referred to as "sensitive" information, defined in the act as, "Any information the loss, misuse, or unauthorized access to or modification of which could adversely affect the national interest or the conduct of Federal programs or the privacy to which individuals are entitled under [the Privacy Act] but which has not been specifically authorized under criteria established by an Executive Order or an Act of Congress to be kept secret in the interest of national defense or foreign policy."

³⁶ *Protection of Third Party Information in Research: Recommendations of the National Institutes of Health to the Office for Human Research Protections*, December 7, 2001. Available at www.nih.gov/signs/bioethics/nih_third_party_rec.html.

Key Concepts: Privacy and Confidentiality

- Data are identifiable when the data elements have personal information that can be linked to subject identity and/or other characteristics that (alone or in combination) could allow the person (research subject) to be identified.
- When an investigator obtains private information about living individuals for research purposes, and the private information retains a link to individually identifying information, the private information ordinarily would be considered individually identifiable to the investigator even when codes are used in lieu of subjects' names or other identifiers.
- According to the Common Rule, IRB review and approval is required for such research, unless it meets one of the exemptions stated at §__.46.101(b).
- The jurisdiction of FDA to regulate human subjects research does not depend on this standard of collection of identifiable information. Therefore, FDA regulations apply regardless of whether the data are identifiable if the activity otherwise falls within the definition of research found in 21 CFR 56.101 and 21 CFR 56.102.
- According to OHRP, research that retains a link to identifying information ordinarily would not be considered human subjects research if, for example, the investigator and research institution do not have access to identifiable private information and a written agreement is obtained from the holder of the identifiable private information that such information will not be released to the investigator under any circumstances.
- The Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (PL 104-191, 110 Stat. 1936) imposes stringent conditions on the uses and disclosures of protected health information. Research that uses health information may be subject to HIPAA if the information is identifiable, is obtained from a covered entity, or is used or disclosed by a covered entity (although not all institutions conducting research are covered entities).
- HIPAA requires that written patient authorization be obtained when protected health information is used or disclosed (unless a waiver of authorization is obtained or another exception exists). This requirement is in addition to the existing rules for obtaining informed consent from research subjects. Neither the scope nor content of a HIPAA authorization is the same as an informed consent document as required under federal regulations.
- HIPAA permits a covered entity to allow investigators to access protected health information in the covered entity's medical records for certain activities that are preparatory to research. Activities that are preparatory to research are those undertaken for the purpose of identifying potential human subjects to aid in the preparation of a protocol or to determine the feasibility of conducting a study.
- The Privacy Rule permits a covered entity to use and disclose protected health information for research without obtaining patient authorization if the information is part of a limited dataset. Covered entities must use a data use agreement to obtain satisfactory assurances that the recipient of the limited dataset will use or disclose the protected health information in the dataset only for specified purposes.
- Under the Privacy Rule, an authorization may be combined with the informed consent document for research. If the informed consent document is combined with an authorization meeting the Privacy Rule's requirements, the Common Rule and FDA regulations would require IRB review of the combined document.
- Privacy Boards do not exercise any of the other powers or authority granted to IRBs under federal laws relating to federally conducted or supported human subjects research and research involving products regulated by FDA.
- Methods commonly employed to protect the confidentiality of research data include the use of codes, honest brokers, encryption methods, and data transfer restrictions.
- During the informed consent process, subjects should receive information about confidentiality issues, including who will have access to the research data and for how long; what further disclosure or data sharing is anticipated; what data security measures will be employed; and what, if anything, will be disclosed to others, by whom, and under what conditions.
- Investigators and IRBs are responsible for ensuring, implementing, and evaluating the efficacy of data protection plans, and institutions are responsible for supporting those plans and their mechanisms for evaluation in a manner that is consistent with existing legal protections.
- Researchers and IRBs should be aware that state laws may impose additional restrictions beyond the Common Rule or FDA regulations. Various state laws limit the release of health information, restrict the uses of genetic information, or confer additional protections for human subjects.
- Certificates of Confidentiality are tools for preventing disclosure of subject identities by investigators.

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Chapter 14

After Initial Review

- A. Introduction
- B. Continuing Review
- C. Outcomes of Institutional Review Board Review
- D. Expedited Continuing Review
- E. Criteria for Requiring Review More Often Than Annually
- F. Determination of the Continuing Review Date
- G. Expiration of Approval Period
- H. Changes in Previously Approved Research
- I. Review of Reports of Unanticipated Problems Involving Risks to Subjects or Others
- J. Review of Data Safety Monitoring Board or Data Monitoring Committee Reports
- K. Suspension or Termination of Institutional Review Board Approval of Research
- L. Consent Monitoring
- M. Independent Verification from Sources Other Than the Investigator That No Material Changes Have Occurred Since the Previous Institutional Review Board Review

Key Concepts

References



A. Introduction

A number of issues can arise after the initial review of a project by an Institutional Review Board (IRB). This chapter explores these issues, including continuing review; criteria for reviewing research more often than annually; expiration of the approval period; review of changes in previously approved research; review of reports of unanticipated problems involving risks to subjects or others or unexpected serious harms to subjects; the role of Data Safety and Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs); suspension or termination of IRB approval; tools for consent monitoring; and verification from sources other than the investigator that no material changes have occurred since the previous IRB review.

B. Continuing Review

The Common Rule and Food and Drug Administration (FDA) human subjects protection regulations require, among other things, that:

- institutions have written procedures that the IRB will follow for
 - conducting its continuing review of research and for reporting its findings and actions to investigators and the institution, and
 - determining which projects require review more often than annually (§____.103(b)(4); 21 CFR 56.108(a));
- each IRB reviews proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in the nonscientific areas (§____.108(b); 21 CFR 56.108(c)) except when an expedited review procedure is used;
- an IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year (§____.109(e); 21 CFR 56.109(f))

Continuing review of research must be substantive and meaningful, not a “rubber stamp” activity. Continuing review by the convened IRB, with a recorded vote on each study, is required unless the research is otherwise appropriate for expedited review (§_____.110; 21 CFR 56.110; see also Chapter 10). The regulations describing review of research do not differentiate between initial and continuing review. Thus, the same substantive considerations described in Chapter 11 for initial IRB review should be applied during continuing review. The procedures for continuing review by the convened IRB may include the use of a primary reviewer system.

In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review, prior to the convened meeting, a protocol summary and a status report on the progress of the research so that the IRB can discuss the protocol adequately and determine the appropriate action. The necessary materials should be listed in the IRB’s standard operating procedures (SOPs).

status report

The status report on the progress of the research should include the following:

- the number of subjects enrolled to date
- a summary of any adverse events and unanticipated problems involving risks to subjects and others
- the number of subjects who have withdrawn from the research or complaints about the research since the last IRB review
- a summary of any recent literature relevant to the research since the last review
- a summary of any interim findings
- a summary of amendments or modifications to the research since the last review
- any relevant multicenter trial reports
- any other relevant information, especially information about risks associated with the research
- a copy of the current informed consent document and any newly proposed consent document

At least one member of the IRB should receive a copy of the complete protocol, including any modifications previously approved by the IRB. Furthermore, upon request, any IRB member should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

When reviewing the current informed consent documents, the IRB should ensure the following: (1) the currently approved or proposed consent document is still accurate and complete and (2) any significant new findings that may relate to the subject’s willingness to continue participation are provided to the subject in accordance with §_____.116(b)(5) and 21 CFR 50.25(a)(5)).

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document. Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

Composition of the IRB

Some institutions designate one or more IRBs for the sole purpose of conducting continuing review. Although such a practice is permissible under the federal regulations for the protection of human subjects, it is important to remember that such IRBs must comply with the membership requirements stipulated in §_____.107 and 21 CFR 56.107.

In particular, FDA and Common Rule requirements require the following for all IRBs, including those that are solely responsible for continuing review:

The IRB shall have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience, expertise, and the diversity of its members, including consideration of race, gender, cultural background, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. For research involving prisoners or incarcerated individuals, a prisoner representative must participate in the review.

It should be noted that the other requirements for IRB membership also apply to IRBs conducting continuing review.

C. Outcomes of IRB Review

The designated IRB must notify investigators and others in the institution in writing of its determinations regarding continuing review (§____.109(d) and §____.115(a)(3),(4); 21 CFR 56.109(e)).

IRB actions that can be taken following review of research include the following:

- Approved with no changes. The research may proceed.
- Approvable with minor changes to be reviewed by the IRB chair or an IRB member(s) designated by the chairperson. Such minor changes must be clearly delineated by the IRB so that the investigator can simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol is approved by the designated reviewer.
- Approvable with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research, unless the research qualifies for expedited review.
- Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating the necessary information.
- Disapproved. The IRB has determined that the research cannot be conducted at the institution or by employees or agents of the institution or otherwise under the auspices of the institution. A protocol can only be disapproved at a convened meeting of the IRB.

Minor changes might include nonsubstantive edits of the consent form for clarification or requests for clarifying information. By contrast, *substantive* changes requiring full IRB consideration might include, for example, suggested changes in sample size or exclusion criteria for enrollment or justification of the sample size or of the study design.

D. Expedited Continuing Review

An expedited review procedure may be used by the IRB to conduct continuing review when the research project involves no more than minimal risk and involves one or more of

conduct continuing review when minimal risk and involves one or more of the specific research categories

the specific research categories listed in Chapter 10. (See also the Department of Health and Human Services [DHHS]-FDA list of research eligible for expedited IRB review published in the *Federal Register* [OPRR 1998].)

When reviewing research under an expedited review procedure, the IRB chairperson or designated IRB member(s) should receive and review the same materials described in Section B above, including the complete protocol.

Generally, if the research did not qualify for expedited review at the time of initial review, it would not qualify for expedited review at the time of continuing review, except in limited circumstances (described by expedited review categories 8 and 9 [OPRR 1998]; see below). It is also possible that research activities that previously qualified for expedited review have changed or will change such that expedited IRB review would no longer be permitted for continuing review.

Expedited Review Category 8

Under category 8, an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows:

- a. Where:
 - 1) the research is permanently closed to the enrollment of new subjects;
 - 2) all subjects have completed all research-related interventions; and
 - 3) the research remains active only for long-term follow-up of subjects;

or

- b. Where no subjects have been enrolled and no additional risks have been identified;

or

- c. Where the remaining research activities are limited to data analysis.

Of note, category 8 identifies three situations in which research that involves greater than minimal risk and that has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multicenter protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category 8 a, b, or c are satisfied for that site. However, with respect to category 8b, although the criterion that “no subjects have been enrolled” is interpreted to mean that no subjects have ever been enrolled at the particular site, the criterion that no additional risk have been identified is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Expedited Review Category 9

Under category 9, an expedited review procedure may be used for continuing review of research not conducted under an Investigational New Drug application or Investigational Device Exemption where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

E. Criteria for Requiring Review More Often Than Annually

Designated IRBs must recognize that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually (§_____.103(b)(4)(ii)). For example, when a new intervention is being tested, the risks may not be completely known. The IRB must monitor the research project closely and may require more frequent review.

The IRB should consider the following factors in determining the criteria for studies that require more frequent review and what the timeframes generally will be:

- the probability and magnitude of anticipated risks to subjects
- the likely medical or psychological condition of the proposed subjects
- the role of the institution and Principal Investigator (PI)
- the overall qualifications and experience of the PI and the research team, including previous non-compliance
- the nature and frequency of adverse events observed in similar research at this and other facilities
- the vulnerability of the population being studied
- other factors that the IRB deems relevant

Other issues might include the design of high-risk studies, such as certain phase 1 clinical trials. Careful analysis of progress to date might be needed before the research continues.

In specifying an approval period of less than one year, an IRB may define the period either by a time interval or by the recruitment of a maximum number of subjects. The Office for Human Research Protections (OHRP) recommends that the minutes of IRB meetings clearly reflect determinations regarding risk and approval period. In addition, the required interval for continuing review must be communicated to the investigator in writing.

F. Determination of the Continuing Review Date

Continuing review must occur by the 12-month anniversary of the initial review, whether at a convened meeting or under expedited review. The “approval date” is when the 1-year clock begins. The “effective date” is when all conditions have been met. The “approval period” is 1-year (from the approval date) minus however long it takes the PI to meet the conditions (effective date). For example:

Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2011. Continuing review must occur by October 1, 2012.

Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2011, and approves the protocol contingent on specific minor conditions the IRB chairperson or his/her designee can verify. On December 31, 2011, the IRB chairperson or designee confirms that the required minor changes were made. Continuing review must still occur by October 1, 2012. In this case the approval period is only 9 months.

Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2011, and has serious concerns or lacks significant information that requires IRB review. At its October 29, 2011, meeting, the IRB completes its review and approves the study. Continuing review must occur by October 29, 2012.

Expedited Review

A study approved under expedited review, must be re-reviewed within one year of the IRB approval date.

Change in Protocol

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review involves review of the full protocol, not simply a change to it.

Review Within 30 Days Before IRB Approval Expires

The Common Rule makes no provision for a grace period extending the conduct of research beyond the expiration date of IRB approval. However, when continuing review occurs within 30 days before the IRB expiration date, the IRB may retain the original expiration.

G. Expiration of Approval Period

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator fails to provide continuing review information to the IRB by the expiration of current approval, the research must stop. However, if the IRB finds that it is in the best interests of individual subjects, then participation may temporarily continue past expiration date. Additionally, the IRB must be allowed time to complete its review and approval before the expiration date.

When continuing review of a research protocol does not occur before the expiration date, IRB approval expires automatically. Enrollment of new subjects cannot occur after the expiration of IRB approval.

H. Changes in Previously Approved Research

Federal regulations also address another circumstance that could occur after initial review (§____110(b); 21 CFR 56.110(b)). Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in PI, the research team, or informed consent documents. No changes may be initiated without prior approval of the IRB, except when necessary to eliminate immediate hazards to subjects.

IRBs may use an expedited procedure to review a proposed change to previously approved research if it represents a minor change that will be implemented within the authorized approval period. IRBs should have written policies describing the basis for defining a minor change. The determination of whether a change is minor should include consideration of the effect of the change on:

expedited review for minor changes

- the level of risk to subjects
- the research design or methodology
- the number of subjects enrolled in the research
- the qualifications of the research team
- the facilities available to support safe conduct of the occur in FDA-regulated drug studies involving human subjects

IRB approval of a minor change in research involving human subjects does not alter the expiration date of the IRB's original approval.

I. Review of Reports of Unanticipated Problems Involving Risks to Subjects or Others

After initial review of research, unanticipated problems must be reported as they occur. The Common Rule at §____.103(b) (5) requires that institutions must have written procedures for ensuring prompt reporting to:

written procedures for unanticipated problems

- the IRB,
- appropriate institutional officials,
- relevant federal agencies, and
- OHRP (for research covered by an applicable OHRP-approved assurance) of any unanticipated problems involving risks to subjects or others

Similarly, FDA regulations at 21 CFR 312.66¹ require that investigators notify the IRB promptly of any unanticipated problems involving risks to subjects or others that occur in FDA-regulated drug studies involving human subjects. FDA regulations also require investigators to report unanticipated adverse device effects to the IRB and sponsor as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The IRB should establish in its SOPs acceptable times for reporting of events that meet regulatory requirements and that reflect the seriousness of the unanticipated problem. It is important to recognize that:

- most adverse events do not represent unanticipated problems involving risks to subjects or others and
- not all unanticipated problems involving risks to subjects or others are adverse events research, or any other factor that would warrant review of the proposed changes by the convened IRB.

Reports to the IRB of unanticipated problems should contain enough information for the designated IRB reviewers to judge whether the event raises new questions about risks to participants. When the study is part of a multisite trial, a standard form may already be in use to provide details of the event to the sponsor. These reports can be forwarded to the designated IRB to provide information about the event. For studies that do not use a standard reporting form, the IRB should specify a format or provide instructions to investigators that describe exactly what information is needed to carry out a substantive review.

¹ See <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>.

The IRB should follow written procedures when reviewing reports of unanticipated problems. Some IRBs rely on the IRB chairperson or another experienced IRB member to review such reports. Some IRBs use a subcommittee, and others review all such reports at convened meetings.

Discussion of unanticipated problems by the convened IRB should be documented in the minutes of the meeting.

The investigator may be asked to make an initial determination about whether (1) the event is related to the research; (2) changes should be made in the protocol or informed consent document; and (3) subjects already enrolled should be informed about the possibility or likelihood of the event or problem. The investigator may submit a change to the consent form or protocol at the same time the adverse event report is submitted. If an event or problem is determined by the IRB reviewer or subcommittee to raise new concerns about risks to subjects to the extent that actions by the convened IRB may be required and changes in the research may be required that are more than minor, the report with the reviewer's or subcommittee's recommendations should be forwarded to all IRB members.

During the convened review of the problem, the IRB should determine whether further action will be required. If so, the IRB's actions may include (1) making a request for further clarification from the investigator; (2) requiring changes to the protocol (e.g., additional tests or visits to detect similar events in a timely way, additional protections for privacy and confidentiality); (3) requiring changes to the consent form; (4) requiring that already-enrolled subjects be informed about the risk of this problem or adverse event; (5) requiring a change in the continuing review period; (6) requiring additional monitoring by the IRB; (7) making further inquiry into other protocols using the particular drug/device/ procedure in question; (8) notifying regulatory agencies; or (9) suspending or terminating the study.

As mentioned above, the institution, usually acting through the IRB chairperson, must provide prompt written notification to relevant federal agencies, including OHRP and FDA (for FDA-regulated research), and to the sponsor and the institutional official, of any unanticipated problems involving risks to subjects or others and of the resolution of those problems.

J. Review of DSMB or DMC Reports

Local IRBs that receive an adverse event report might not always be able to determine whether the event is frequent or rare, whether it is caused by the research as opposed to an underlying illness or standard treatment, or whether the adverse event is more common in the intervention group than in the control groups. Moreover, the IRB might lack access to the essential data needed to evaluate adverse event reports. In recent years, entities other than the IRB, such as DSMBs or DMCs have begun to play an increasingly important role in safety. (Henson 2009) These committees may be well situated for safety monitoring because they review data from all participating sites and have access to unblinded data. FDA tends to call such committees DMCs, (FDA 2006) while the National Institutes of Health (NIH) refers to them as DSMBs.

DSMBs/DMCs were initially used primarily in large randomized multicenter trials that targeted improved survival or reduced risk of major morbidity as the primary objective and that were sponsored by federal agencies such as NIH and the Department of Veterans Affairs in the United States and by similar bodies abroad.

FDA Policy

According to FDA regulations, sponsors are required to monitor studies evaluating new drugs, biologics, and devices (see 21 CFR 312.50 and 312.56 for drugs and biologics, as well as 21 CFR 600.80, and 21 CFR 812.40 and 812.46 for devices). Various individuals and groups play different roles in clinical trial monitoring. In the context of FDA, a DMC may be appointed by a sponsor to evaluate the accumulating outcome data in some trials. The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. Many different models have been proposed and used for the operation of DMCs.

**safety
monitoring**

According to FDA, all clinical trials require safety monitoring (21 CFR 312.32(c)), but not all trials require monitoring by a formal committee external to the trial organizers and investigators.² As noted earlier, DMCs have generally been established for large, randomized multisite studies that evaluate interventions intended to prolong life or reduce the risk of a major adverse health outcome. Because monitoring of accumulating results is almost always essential in such trials DMCs should be established for controlled trials with mortality or major morbidity as a primary or sec-

**multisite
clinical trials**

² The only FDA regulation that requires the use of a Data Monitoring Committee is 21 CFR 50.24, FDA's exception from informed consent requirements for emergency research. The FDA issued guidance in 2006. See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm>.

ondary endpoint. They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study. Several factors are relevant to determining whether or not to establish a DMC for a particular trial. These relate primarily to safety, practicality, and scientific validity.

If a DMC establishes a causal relationship between some serious adverse events and an investigational intervention, such findings should be conveyed to the sponsor, and the sponsor would be required to report them to FDA and to all study investigators, according to 21 CFR 312.32 (drug trials) and 21 CFR 812.150(b)(1) (device trials). Study investigators are generally responsible for reporting such findings to their IRBs, according to 21 CFR 312.66 (drug trials) and 21 CFR 812.150(a)(1) (device trials), although direct reporting from sponsors to responsible IRBs may be arranged and may be preferable in some situations (for example, when a central IRB has been established). For a device trial, however, the sponsor is clearly responsible for notifying all participating IRBs of unanticipated adverse events (21 CFR 812.150(b)(1)).

In addition, sponsors should notify FDA and the responsible IRBs of any recommendations or requests made by a DMC to the sponsor that address safety of participants—for example, recommendations to lower the dose of a study agent because of excess toxicity or to inform current and future trial participants of an emerging safety concern that had not been recognized at the start of the trial. Such recommendations would always be presumptively based on findings that would meet the definition of a serious and unexpected adverse event. When mutually agreed to by the sponsor and the DMC, a DMC may be delegated responsibility for reporting directly to FDA, although in most cases the sponsor will make such reports.

NIH Policy

It is NIH policy that each of its institutes and centers has a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of subjects and the validity and integrity of the data for all NIH-supported or conducted clinical trials.³ The establishment of DSMBs is required for multisite clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an

IRB. The NIH policy states the following:

Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); and efficacy, effectiveness and comparative trials (phase III).

Monitoring should be commensurate with risks. The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.

Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

Beginning in October 2000, NIH also required that investigators submit a monitoring plan for all clinical trials to the funding unit as part of the research application. This plan is reviewed by the scientific review group, and any comments and concerns are included in an administrative note in the summary statement.⁴

OHRP Policy

In a separate but related policy, OHRP has issued guidance stating that, when DSMBs/DMCs are used, an IRB conducting continuing review of research can rely on a current statement from the DSMB/DMC, indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its

³ See <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

⁴ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.

continuing review is substantive and meaningful.

Role of Data and Safety Monitoring

Before it can approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision for data monitoring in order to ensure the safety of subjects (§____.111(a)(6); 21 CFR 56.111(a)(6)). When research risks are substantial, a general description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting serious unexpected adverse events.

In general, it is desirable for the study sponsor to establish a DSMB/DMC for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions. For some studies, NIH requires a DSMB/ DMC. The IRB has the authority to require a DSMB/DMC as a condition for approval of research when it determines that such monitoring is needed.

When DSMBs/DMCs are used, IRBs conducting continuing review of research may rely on a current statement from the DSMB/DMC indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

K. Suspension or Termination of IRB Approval of Research

An IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects (§____.113; 21 CFR 56.113). The regulations also require that the IRB must notify the PI in writing of such suspensions or terminations and should include a statement of the reasons for the IRB's actions. The investigator should be provided with an opportunity to respond in person or in writing. As described above, IRBs operating in accordance with the Common Rule must have written policies and procedures for such reporting in place that must be followed in these circumstances (§____.103(b)(5); 21 CFR 56.108(b)(s)).

L. Consent Monitoring

IRBs have the authority to observe, or have a third party observe, the consent process and the research. Thus, IRBs have considerable power to monitor events related to subject risk and safety between formal IRB reviews. Consent monitoring is one way to help assure that the rights and welfare of individuals participating as subjects in research are protected, following the approval of a project by the IRB. In considering

the adequacy of informed consent procedures, IRBs may require special monitoring of the consent process by an impartial observer (consent monitor) to reduce the possibility of coercion and undue influence.

Such monitoring may be especially warranted in cases where the research presents significant risks to subjects or where subjects are likely to have difficulty understanding the information to be provided—for example, if there were a language barrier. Monitoring also may be appropriate as a corrective action when the IRB or a federal agency has identified problems associated with a particular investigator or a research project.

M. Independent Verification from Sources Other Than the Investigator That No Material Changes Have Occurred Since the Previous IRB Review

Sometimes to help ensure subject safety, it may be necessary for an IRB to require independent verification from sources other than the investigator that no material changes have occurred since the previous IRB review. IRBs are required to have written procedures for determining which protocols need such verification (§____.103(b) (4); 21 CFR 56.108(a)). OHRP recommends that such written procedures include the specific criteria used to make these determinations (for example, such criteria could include some or all of the following: (1) randomly selected projects; (2) complex projects involving unusual levels or types of risk to subjects; (3) projects conducted by investigators who previously have failed to comply with the requirements of the DHHS regulations or the requirements or determinations of the IRB; and (4) projects where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources).

IRBs may consider the following factors in determining which studies require independent verification:

- the probability and magnitude of anticipated risks to subjects
- the likely medical or psychological condition of the proposed subjects
- the probable nature and frequency of changes that may ordinarily be expected in the type of research proposed
- the prior experience (including lack of or negative) with the PI and the research team
- other factors that the IRB deems relevant

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or it may retrospectively require such verification at the time of

Key Concepts: After Initial Review

- An IRB is required to conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk but not less than once per year.
- Expedited review is permitted if research is minimal risk and is covered by one or more categories on the DHHS-FDA list of research eligible for expedited IRB review (published in the Federal Register).
- The designated IRB must notify investigators and other points of contact in the institution in writing of its determinations.
- IRBs may require continuing review more frequently than once per year, depending on criteria that are relevant to the degree of risk to research subjects.
- IRBs may use expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented within the authorized approval period.
- After initial review there may be unanticipated problems or adverse events from the research that must be considered and reported. Changes in consent or protocol may be warranted based on adverse events.
- DSMBs or DMCs may be used to review events during the course of a research protocol.
- All investigators conducting research under the Common Rule must promptly notify their designated IRBs of serious adverse events or unanticipated problems involving risks to subjects or others, and the IRBs have an important role in following up on these reports.
- Institutions and IRBs are empowered to monitor events related to the risks to and safety of subjects.

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Chapter 15

Cooperative Research and Research Involving Multiple Institutions

- A. Introduction
 - B. Current Requirements
 - C. Review of Multisite Studies
 - D. Communication and Record-Keeping Issues
 - E. Advantages of Joint or Ceded Review of Collaborative Research
- Key Concepts**
References



A. Introduction

In the United States, independent review of research involving human subjects primarily occurs at the local level. The development of local review grew out of the peer review process used to evaluate scientific merit and the National Institutes of Health (NIH) requirement that grantee institutions take responsibility for the ethical conduct of human research (NBAC 2001). It is a model of review that reflects the nature of research at the time it was developed—single research studies conducted by one investigator from a single institution. Local institutional review was seen as offering distinct advantages, and, in its early evaluation of the Institutional Review Board (IRB) system, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) supported the use of “local review committees...located in institutions where research is conducted” (National Commission 1978,1).

The rapid growth of collaborative studies, particularly involving multisite, multi-institutional clinical trials, sometimes challenges the ability of local scientific review committees and IRBs to meet their responsibilities efficiently and effectively. Although most collaborative studies occur at multiple institutions, investigators from different institutions might collaborate in conducting research at a single site. Research of all types can be conducted cooperatively and can involve hundreds of institutions. In these collaborations, each institution might perform experimental interventions

(e.g., clinical trials) or simply provide investigators access to data (e.g., epidemiological studies), or institutions might all perform the same or different functions (e.g., one institution collects tissue samples, another analyzes them), or institution may be geographically proximate or on different continents.

Some cooperative research may involve investigators or institutions such as a single community physician, a small private practice, or a small hospital or college that rarely conduct research and have insufficient resources or expertise to establish their own IRBs. In some cases, these may rely on an IRB at a neighboring institution, which could provide some degree of local review because of its familiarity with the community from which the subjects come, although it would not necessarily be familiar with the investigators or the circumstances under which the research would be conducted.

In recent years, many analysts have noted that multisite review of multisite research has become a cumbersome and labor-intensive process, because in most cases each research organization’s IRB considers the same protocol, performs the same risk assessment, examines the same or similar consent form, and later reviews the same, often voluminous, set of adverse event reports (IOM 2003; NBAC 2001). Some reviews of the system have found that IRBs can be frustrated by spending scarce resources on reviewing the same research protocol that, in some cases, is being

reviewed by hundreds of other IRBs, even when overall design and methods can only be changed with great difficulty (NBAC 2001). In addition, multisite review can introduce considerable variability into the approvals and/or required modifications to study design or disclosure language, which could actually detract from subject protections. Moreover, some believe that in some cases the review of multisite studies by each organization participating in a study might not necessarily increase the level of protection provided to research subjects or enhance the scientific design of the protocol.

Even the National Commission eventually recognized that in some cases research studies did not require review by an IRB located in or near the institution where the research would be conducted. For multisite research studies, the National Commission stated as follows:

Review by one IRB (generally at the entity most substantially involved with the research) should satisfy statutory and regulatory requirements. Other entities that are involved with the research may also require review by their IRBs, however. In such instances, IRBs should give priority to consideration of protocols that are receiving multiple reviews, in order to reduce the extended time period that such review may entail (National Commission 1978, 8).

Considerable flexibility exists within the regulatory framework for accommodating cooperative research efforts. However, individual research organizations are not always willing to cede review and oversight to an off-site board because of concerns about institutional liability, despite flexibility in the regulatory requirements.

This chapter addresses the regulatory framework regarding responsibilities of the human research protection program (HRPP) in the review and oversight of cooperative research and research involving multiple sites, and it provides some examples of models for review of multisite research.

B. Current Requirements

Within today's regulatory framework, each institution engaged in cooperative research covered by the Common Rule must provide a written assurance of compliance with the regulations satisfactory to the supporting federal department or agency head and certify to the supporting department or agency that the application or proposal for research has been reviewed and approved by an IRB designated in the assurance (§____.103(a),(b),(f)).

However, the Common Rule at §____.114 (Cooperative Research) states, in part, that "in the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with the Common Rule. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort." In practical terms, this policy states that each institution engaged in cooperative research must have its own IRB review the research protocol or make other arrangements for review, which must be approved by the department or agency head (thus, an institution can cede authority for the review). For example, an institution that does not have its own IRB could use an IRB from another institution or an independent IRB to review its research. In general, when an institution relies on the review of an IRB at another institution, that IRB must be designated under the institution's assurance of compliance. However, some federal funding agencies, for example, the Department of Veterans Affairs, do not allow this arrangement.

**joint review
arrangements**

This requirement is imposed on IRBs that must follow the Common Rule, but it is not imposed on IRBs that must comply only with the Food and Drug Administration (FDA) regulations, which do not require that all institutions or individuals engaged in the research have their IRBs review

<p style="text-align: center;">The Common Rule §____.114</p>	<p style="text-align: center;">FDA Regulations 21 CFR §56.114</p>
<p>Each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with the Common Rule. With the approval of the Department or Agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.</p>	<p>Cooperative research/multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of effort.</p>

the research protocol. Likewise, since 1981 FDA has allowed nonlocal review of research (review by an IRB geographically remote from the research site and/or independent of the institution conducting the research), as long as the IRB obtains sufficient knowledge of the local research context for each research site (21 CFR 56.107, 56.111(a)(3),(a)(7),(b); FDA 1998). The nonlocal IRB needs to ensure that these requirements are met for each location for which it has assumed IRB oversight responsibility.

Thus, although IRBs must have knowledge of the local research context, there are no regulatory requirements that preclude review by IRBs that are not organizationally part of the institutions conducting research and/or are not geographically close to the research site. What is required, however, is that the IRB should have sufficient knowledge of the local research context—in terms of the relevant institutions, the relevant investigators, and the relevant communities—to conduct an effective review (§____.107(a) and §____.111(a)(3)-(4); 21 CFR 56.107(a)).

The Common Rule and the FDA regulations require all IRBs to have membership that is sufficiently qualified to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects (§____.107(a); 21 CFR 56.107). IRBs conducting nonlocal review need to be knowledgeable about the community from which the subjects are drawn in order to ensure that subject rights will be protected and that the consent process is appropriate for the subject population involved. The IRB should be sensitive to community laws and mores, because state and local laws and community attitudes pertaining to research may be more restrictive than federal regulations or the prevailing standards of the community where the IRB is located.

IRBs can obtain knowledge of the local research context, including community attitudes, through a site visit by a representative of the IRB, by appointing an IRB member from that community, or by having a consultant from the community advise the IRB, either prior to or during the deliberations. If travel is not feasible, participation in the IRB meeting can be by video conference or conference telephone call or through the use of other technologies that allow for real-time conversational interaction between the remote member and the members at the convened location. All IRB members should receive an advance copy of the documents that are to be reviewed at the meeting. The minutes of the meeting during which nonlocal research is reviewed should document the procedures used to assure that community attitudes were adequately taken into consideration.¹

In 1995, the Office for Protection from Research Risks (OPRR) began approving assurances in which an institution designates an independent IRB (that is, freestanding and not affiliated with the research institution) (DHHS OIG 1998). In recent years, guidance from the Office for Human Research Protections (OHRP) also has moved in the direction of joint or ceded review in collaborative research; however, OHRP has emphasized the types of local knowledge that may be required for different types of studies. OHRP allows “institutional sites that are geographically close enough to comfortably contribute membership to a common IRB” to create such a shared, or common, IRB.² Recently, OHRP has approved a program using a central IRB for the review of certain National Cancer Institute (NCI)-funded cooperative cancer trials and a cooperative review arrangement by a group of geographically disparate institutions. OHRP also has joined FDA in accepting IRBs that routinely meet by teleconference, facilitating the work of IRBs whose members are truly representative of various geographic areas.³

One issue that concerns some adherents to the concept of local review is the effect of remote review on the adequacy of the consent process. However, geographically remote IRBs should be able to ascertain the basic demographic characteristics of a community from afar, noting that institutions that enroll participants from a defined geographic community might not enroll participants from a single cultural community. There are, of course, a few cases in which geographically cohesive groups have readily identifiable beliefs relevant to the interests of research subjects (e.g., some American Indian communities), but these cases appear to be the exception rather than the rule (Norton and Manson 1996; Sharp and Foster 2000).

Nonetheless, institutions and/or IRBs that serve diverse communities must be attentive to the information needs of subjects from various cultural backgrounds, even as local variability in, for example, language and educational attainment influences IRB review of protocols.

C. Review of Multisite Studies

Local institutions must be able to maintain some oversight over the research their investigators conduct, and each institution must decide whether it wants to participate in a multisite research study. Moreover, individual institutions must maintain the authority to decline to participate in a study, even if another IRB has approved the research. Local IRBs should reserve the right to refuse the primary review body's determination regarding serious safety concerns and unique local requirements.

¹ See www.fda.gov/oc/ohrt/irbs/nonlocalreview.html.

² General Guidance on the Use of Another Institution's IRB. August 9, 1991. Available at www.hhs.gov/ohrp/humansubjects/guidance/irb-rely.htm.

³ IRB Meetings Convened via Telephone Conference Call. March 28, 2000. Available at www.hhs.gov/ohrp/references/irbtel.pdf.

As long as an accredited IRB reviews and approves the research protocol, multiple IRB reviews of the same research protocol are not always necessary to ensure the protection of research participants. For research studies conducted solely by one institution, it often makes sense for that institution's IRB to conduct the review, but, for cooperative research, IRB review by all institutions participating in the research may be unnecessary.

A number of arrangements between a local institution and the reviewing IRB could be possible. The reviewing or lead IRB might be, for example, the IRB of the institution where the research study was developed, an IRB at a participating institution with particular expertise in the areas of research, or an independent IRB. It is essential that the terms of the arrangement be clearly defined in advance with respect to the roles and responsibilities to be assumed by each party. It must be clear who will have responsibility for:

- providing ongoing educational programs for investigators and staff
- conducting appropriate verification activities
- addressing subjects' complaints and concerns
- bringing local knowledge and standards to bear on IRB review (NBAC 2001)

Members of the local IRB could provide knowledge about the community in which the research would be conducted to the external or lead IRB during its review or by assessing the decisions of the lead IRB as part of local control. Alternatively, the local IRB might arrange to have the option of tailoring the consent process and documentation to the needs of the local institution and participants.

In 1992, OPRR issued guidance for NIH multicenter clinical trials that include NIH-approved sample informed consent documents. The guidance also required that each local IRB receive a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB and, when appropriate, the sponsor. In addition, the justification for and approval of such deletions or modifications must be reflected in the IRB minutes. For trials sponsored by NCI, investigators must forward copies of such IRB-approved changes, with their justifications, to all appropriate parties. Thus, for NIH-sponsored trials, consent forms modified by a local IRB must be recorded.

In the case of a lead or central IRB, the organization with primary responsibility for obtaining the assurances also

should assume the responsibility for acting decisively should violations occur, including termination of the study or the site and/or reporting violations and violators to authorities.

In 2003, the Institute of Medicine (IOM) noted that for FDA-regulated trials, it should not be assumed that the industry sponsor has primary responsibility for the program; it would be preferable for the research institutions involved to share that responsibility, because they are most directly and closely involved with the research subjects (IOM 2003). In addition, determinations regarding potential financial conflicts of interest should be forwarded to the lead IRB by the appropriate entity (i.e., the party responsible for the oversight of an investigator's role in a project).

FDA Draft Guidance

In January 2005, FDA issued draft guidance for industry using a centralized IRB review process in multicenter clinical trials.⁴ This guidance is intended to help facilitate IRB review of multicenter research using a centralized IRB review process (a single central IRB or a small number of central IRBs) in situations where centralized review would not compromise human subject protections and could improve efficiency.

The guidance document (1) describes the roles of the participants in a centralized IRB review process, (2) offers guidance on how a centralized IRB review process might consider the concerns and attitudes of the various communities participating in a multicenter clinical trial, (3) makes recommendations about documenting agreements between a central IRB and the IRBs at institutions involved in the centralized IRB review process concerning the responsibilities of a central IRB and each institution's IRB, (4) recommends that IRBs have procedures for implementing a centralized review process, and (5) recommends how a central IRB should document its reviews of clinical trial sites not affiliated with an IRB. This guidance applies to clinical investigations conducted under 21 CFR Part 312 (Investigational New Drug Application or IND regulations). The reader is encouraged to consult the FDA Web site regarding the status of this guidance document.

D. Communication and Record-Keeping Issues

The agreement for IRB review of cooperative research should be documented. Depending on the scope of the agreement, documentation may be simple, in the form of a letter, or more complex, such as a formal Memorandum of Understanding. In the case of studies supported or conducted by the Department of Health and Human Services

⁴ See www.fda.gov/cber/gdlns/irbclintrial.htm.

(DHHS), arrangements or agreements may be subject to approval by DHHS through OHRP and should be executed in accordance with OHRP's instructions. Whatever form of documentation is used, copies should be furnished to all parties to the agreement and to those responsible for ensuring compliance with the regulations and the IRB's determinations. The IRB's records should include documentation of such agreements.

All of the record-keeping requirements addressed in the regulations apply to the IRB that reviews research on behalf of multiple institutions in the case of collaborative research (21 CFR 56.115; 21 CFR 56.115) (see also Chapter 9). However, any time one institution designates the IRB of another institution to review cooperative or multisite research, lines of communication between all involved institutions must be unambiguous and open at all times.

record keeping requirements

When an IRB approves a study, it notifies (in writing) the investigator and the institution at each location for which the IRB has assumed responsibility (§ 56.109(d); 21 CFR 56.109(e)). All required reports from the investigators should be sent directly to the responsible IRB with copies to the investigator's institution, as appropriate.

The IRB of record has a duty to report the following to other IRBs or institutions participating in the research:

- any unanticipated problems involving risks to human subjects or others
- any instance of serious continuing noncompliance with the regulations or the requirements or determinations of the IRB
- any suspension or termination of IRB approval

An appropriate individual, such as the IRB administrator, is responsible for corresponding with the other interested entities concerning the status of research under review by the IRB. It would be appropriate to communicate regularly and appropriately with the other sites about all study-related issues. In the case of FDA-regulated research, appropriate team members of the IRB administrator should communicate regularly with the sponsor about the status of the research. Important conversations among sites should be documented, perhaps in a telephone contact log. All sites should keep originals or photocopies of all relevant documentation (e.g., protocol, consent forms, IRB approval). Although all participating research organizations should be kept abreast of the status and progress of studies, it is important to keep the reporting burden reasonable for the IRB of record.

E. Advantages of Joint or Ceded Review of Collaborative Research

Increasingly, large multisite clinical trials in the United States—both publicly and privately sponsored—are being formed, providing experience for institutions. For several years, the United Kingdom has relied on regional committees for review of multisite research, and Denmark handles multisite studies by assigning the review responsibility to a lead committee (Alberti 2000; Holm 2001). These approaches can reduce duplicative workloads and assure that reviews take place in settings that can bring to bear the appropriate scientific and ethical expertise. For example, complex protocols may involve consulting with biostatisticians, epidemiologists, and clinical specialists who might not be available at some individual sites (IOM 2003).

The ability to distribute costs also could place a regional program in a better position to provide the resources and infrastructure needed for various functions, such as maintaining qualified monitors for research that is higher risk. Furthermore, by ceding certain responsibilities to a regional unit, local programs could direct their efforts and resources to the remaining single-site studies for which they are responsible. This might be particularly useful to research organizations that have few resources, including small academic centers and community hospitals (IOM 2003).

In addition, regional or centralized review could provide a cost-effective alternative to smaller institutions and study sites that cannot afford to maintain a sufficiently comprehensive program on-site. Such organizations, for example, may find it difficult to sustain IRBs with the associated increased costs for training, monitoring, and, increasingly, accreditation preparation and the associated fees.

Key Concepts:

Cooperative Research and Research Involving Multiple Institutions

- Considerable flexibility exists within the regulatory framework for accommodating cooperative research efforts. However, individual research organizations are not always willing to cede review and oversight to an off-site board because of concerns about institutional liability.
- The Common Rule at §____.114 states that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with the Common Rule. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.
- FDA regulations at 21 CFR 56.115 state that “cooperative research/multi-institutional studies may use joint review, rely upon the review of another qualified IRB, or similar arrangements aimed at avoiding duplication of effort.
- Local institutions must be able to maintain some oversight over the research their investigators conduct, and each institution must decide whether it wants to participate in a multisite research study. Local IRBs should reserve the right to refuse the primary review body’s determination regarding serious safety concerns and unique local requirements.
- In multisite collaborative research, it is essential that the terms of the arrangement be clearly defined in advance with respect to the roles and responsibilities to be assumed by each party.
- The IRB administrator for the central or lead IRB is responsible for corresponding with the other interested entities concerning the status of research under review by the IRB.
- In the case of FDA-regulated research, appropriate team members of the IRB administrator should communicate regularly with their sponsor about the status of the research. Important conversations among sites should be documented, perhaps in a telephone contact log.
- Although all participating research organizations should be kept abreast of the status and progress of studies, it is important to keep the reporting burden reasonable for the IRB of record.

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Chapter 16

Food and Drug Administration-Regulated Research

- A. Introduction
 - B. Shared Responsibilities for the Protection of Human Subjects
 - C. Exceptions from the Requirements for Institutional Review Board Review and Informed Consent
 - D. Financial Interests
 - E. Investigational New Drug Application
 - F. Investigational Device Exemption
 - G. Food and Drug Administration Inspection of Biomedical Research
- Key Concepts**
References



A. Introduction

The U.S. Food and Drug Administration (FDA) regulates the conduct of clinical investigations that support research and marketing applications for all FDA-regulated products (foods, drugs, biological products, therapeutic and diagnostic medical devices, and veterinary products). FDA's responsibility extends to such studies regardless of their source of funding, their location within the United States, or the purpose for which they are conducted (e.g., for commercialization of the product or to advance scientific knowledge). FDA regulations for the protection of human subjects (21 CFR Part 50—Protection of Human Subjects and 21 CFR Part 56—Institutional Review Boards) were harmonized in many but not in all ways with the Common Rule, which governs the protection of human subjects in federally conducted and funded research, to the extent permitted by FDA's statute and mission. If a federally funded study involves an FDA-regulated product and the federal agency was a signatory to the Common Rule, then both FDA's regulations and the Common Rule apply.

This chapter summarizes the shared roles and responsibilities of FDA, sponsors, researchers, Institutional Review Boards (IRBs), and others in protecting human subjects who participate in research involving investigational products under FDA's jurisdiction and provides other FDA-specific information of interest to IRBs. FDA's regulations for the conduct of clinical studies include:

- Protection of Human Subjects (21 CFR Part 50)¹
- IRBs (21 CFR Part 56)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Investigational New Drug Applications (INDs) (21 CFR Part 312)
- Investigational Device Exemptions (IDEs) (21 CFR Part 812)

The applicability of the Common Rule and FDA's human subjects protection regulations are discussed at length in Chapter 3. Although the Common Rule and FDA's regulations for informed consent and IRBs are essentially congruent, there are some differences resulting from the differences in statutory authority and mission. FDA's regulations are promulgated to implement the Federal Food, Drug, and

¹ 21 CFR Part 50 Subpart A discusses General Provisions; Subpart B discusses Informed Consent of Human Subjects; and Subpart D discusses Additional Safeguards for Children in Clinical Investigations.

Cosmetic Act,² and they carry the force of law. These regulations describe the minimum requirements that must be accomplished in order to be in compliance with the law.

B. Shared Responsibilities for the Protection of Human Subjects

Although the IRB is primarily responsible for reviewing research to assure the protection of the rights and welfare of human subjects, others have key roles in ensuring the ethical conduct of research (see Chapter 1; IRB responsibilities are described in Chapter 3). Although the Common Rule and FDA's human subjects protection and IRB regulations address the responsibilities of IRBs and institutions in protecting research subjects, FDA regulations also specify detailed responsibilities for clinical investigators and sponsors of research in the area of drugs, biologics, and medical devices.

Clinical Investigator Responsibilities

A clinical investigator is the individual who actually conducts a clinical investigation—that is, the individual under whose immediate direction the drug, biologic, or medical device is administered or dispensed to a subject or, for a medical device, is used involving a subject.

The clinical investigator's responsibilities are described in 21 CFR Part 312 for drugs and biologics. A number of these responsibilities are listed on the Form FDA-1572,³ which is used by sponsors to provide documentation that the clinical investigator and the site have the necessary qualifications to conduct the study. The sponsor uses FDA-1572 to obtain:

1. Specific information from the clinical investigator about the study⁴; and
2. The clinical investigator's commitment that he/she will comply with all of the regulatory requirements for the conduct of the study.

In the case of medical devices, a signed investigator agreement is used instead of FDA-1572 (21 CFR Part 812). This agreement essentially prescribes the same responsibilities as those contained **FDA 1572** on FDA-1572; however, there is no set form. The responsibilities included in this agreement are outlined in 21 CFR Part 812. By signing these agreements, the clinical investigator promises, among other things, to

- conduct the study in accordance with the relevant current protocol and make changes only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
- comply with all requirements regarding the obligations of clinical investigators and all other pertinent regulatory requirements;
- inform any potential subjects that the drugs/devices are being used for investigational purposes;
- ensure that the requirements for obtaining informed consent are met (21 CFR Part 50);
- ensure that the requirements for IRB review and approval are met (21 CFR Part 56);
- report to the sponsor adverse experiences that occur in the course of the investigation;
- ensure that all associates and employees assisting in the conduct of the study are informed about their obligations in meeting these commitments;
- promptly report all changes in the research activity and all unanticipated problems involving risks to human subjects or others to the IRB and not make any changes in the research without IRB approval, except where necessary to eliminate immediate hazards to the human subjects; and
- identify all of the subinvestigators who will be assisting the investigator with the research.

FDA does not require FDA-1572 to be submitted to the agency, although many sponsors send the form to FDA as a convenient way of providing information required by FDA regulations. For example, FDA-1572 and 21 CFR §312.23(a)(6)(iii)(b) require the name, address, and a

Relevant FDA regulations may be accessed by clicking on "regulations" in the middle column of the Good Clinical Practices (GCP) web site, www.fda.gov/oc/gcp. Guidance also is available there. Alternate methods to those specified in FDA's guidance documents may be used to achieve compliance with the regulations. FDA has developed a number of guidance documents (including information sheets) to help IRBs and clinical investigators understand FDA regulations. These are posted on FDA's web site. Questions may be e-mailed to gcpquestions@oc.fda.gov.

² The Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA), PL 75-717 (June 25, 1938) is the basic authority intended to ensure that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive. It has been amended numerous times since its enactment.

³ Form FDA-1572 is available on-line at www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf.

⁴ For example, the name and address of the facility or facilities where the clinical investigation will be conducted, the name and address of the IRB responsible for reviewing and approving the study, or the name and address of any clinical laboratory facilities to be used in the study.

statement of qualifications for each investigator and any subinvestigators who will assist the investigator in conducting the study, the name of the facilities at which the research will take place, and the name and address of the IRB that will review the study.

Other responsibilities of clinical investigators that are described in the regulations include, but are not limited to:

- preparing and maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual to whom the test article⁵ is administered or employed as a control in the investigation;
- ensuring that he/she will administer the test article only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator;
- ensuring that he/she will not supply the test article to any person not authorized to receive it;
- maintaining adequate records of the disposition of the study drug or medical device, including dates, quantity, and use by the study subjects;
- allowing FDA to inspect and copy any records and reports pertaining to the study.

Sponsor Responsibilities

A *sponsor* is defined as the person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, a pharmaceutical company, a government agency, an academic institution, or a private organization. The sponsor does not actually conduct the study unless the sponsor is a sponsor-investigator (21 CFR §§312.3 and 812.3(o)).

A *sponsor-investigator* is an individual who both initiates and conducts an investigation and under whose immediate direction the test article is administered or dispensed. Sponsor-investigators must comply with the regulations that apply to both sponsors and investigators (21 CFR §§312.3 and 812.3(o)).

**sponsor-
investigator**

All of the sponsors' responsibilities for conducting clinical studies of drugs and biologics are set forth throughout 21 CFR Part 312. These include, but are not limited to:

- submitting an IND to FDA if the sponsor intends to conduct a clinical investigation (see 21 CFR §312.23 for IND content and format; INDs are discussed later in this chapter);
- waiting until the IND is in effect before shipping the investigational drug to the clinical investigator to begin the investigation;

- amending the IND and maintaining the IND as needed to ensure that the clinical investigations are conducted according to protocols included in the application (21 CFR §312.30);
- reviewing all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source;
- filing annual reports to summarize the status of each study in progress and each study completed during the previous year, including clinical and nonclinical investigations;
- continually updating essential information on the IND that is not within the scope of protocol amendments, IND safety reports, or annual reports;
- selecting investigators who are qualified by training and experience as appropriate experts to investigate the drug;
- providing the clinical investigators with the information to conduct an investigation properly;
- ensuring proper monitoring of the investigation;
- ensuring that the investigation is conducted in accordance with the investigational plan and protocols contained in the IND;
- maintaining an effective IND with respect to the investigation;
- ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug; and
- ensuring the return or proper disposal of any unused supplies of the investigational drug.

Sponsors' responsibilities for the conduct of medical device studies are set forth in 21 CFR Part 812. Sponsors of medical device studies are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigations properly, ensuring proper monitoring of the investigations, ensuring that IRB reviews and approvals are obtained, submitting IDE applications to FDA, and ensuring that any reviewing IRBs and FDA are promptly informed of significant new information about the investigations (21 CFR §812.40). (IDEs are described later in this chapter.)

FDA's financial disclosure regulation requires all sponsors to certify to the absence of financial interests or disclose information regarding the financial interests of clinical investigators who conduct covered studies for the sponsor (21 CFR Part 54). (For more information concerning financial interests, see Section D of this chapter and Chapter 22.)

⁵ A test article is any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the FFDCRA or under sections 351 and 354-360F of the Public Health Service Act (21 CFR 50.3(j)).

If a sponsor discovers that an investigator is not complying with the investigator's agreement (FDA-1572 or other agreement [for device studies]), the investigational plan, or FDA's regulations for the conduct of the study, the sponsor is required to secure the investigator's compliance. If the sponsor is unable to secure compliance, the sponsor is required to terminate the investigator's participation in the investigation, discontinue shipments of the test article to the investigator, and have the investigator dispose of or return any remaining stock of the test article to the sponsor. For

drugs and biologics

clinical investigations involving drugs or biologics, the sponsor is also required to report the termination to FDA. For more information, see 21 CFR §312.56(b) and 21 CFR §812.46(a).

Clinical investigations of drugs and biologics require that sponsors also:

- maintain records showing the receipt, shipment, or other disposition of the investigational drugs
- maintain records of any financial interests of the clinical investigator in the study or payments made to the clinical investigator by the sponsor of the study
- reserve samples of any test articles and reference standards identified in and used in any bioequivalence or bioavailability studies

Sponsors must retain all required records and reports for two years after the marketing application is approved for the drug or, if an application is not approved, for two years after shipment and delivery of the drug for investigational use is discontinued and FDA has been notified. Sponsors must permit FDA to have access to and copy and verify any records and reports related to clinical investigations (21 CFR §312.57).

Clinical investigations of medical devices require that sponsors maintain:

medical devices

- records of shipment and disposition, including the name and address of the consignee, type and quantity of the device, date of shipment, and batch numbers or code marks
- signed investigator agreements including the financial disclosure information that must be collected under 21 CFR Part 54
- records pertaining to "nonsignificant risk" devices
- records concerning adverse device effects
- any other records required by FDA regulations or by specific requirements for a category of investigation or a particular investigation

Sponsors must retain all required records and reports for two years after the later of the following two dates—the date on which the investigation is terminated or completed or

the date that the records are no longer required—for purposes of supporting a premarket approval application or a notice of completion of a product development protocol (21 CFR §812.140). Sponsors must permit FDA to have access to and copy and verify any records and reports related to clinical investigations (21 CFR §812.140(b)(4)).

Transfer of a Sponsor's Responsibilities to a Contract Research Organization Under 21 CFR §312.52

A sponsor may transfer any or all of the sponsor's responsibilities to a contract research organization (CRO). A CRO is defined in 21 CFR §312.3(b) as a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor—for example, the design of a protocol, the selection or monitoring of investigations, the evaluation of reports, and the preparation of materials to be submitted to FDA. If the sponsor transfers obligations to a CRO, it must be done in writing, and the sponsor must describe each of the obligations being assumed by the CRO, particularly if not all obligations are transferred. Any obligation that is not included in the written description is deemed not to have been transferred. If all responsibilities are transferred, then a general statement to that effect is acceptable (21 CFR §312.52(a)).

Reports of Unanticipated Problems Involving Risks to Subjects or Others

IRB Responsibilities. IRB responsibilities for following written procedures to ensure prompt reporting of unanticipated problems involving risks to subjects or others to the IRB, institution, and FDA are described in detail in Chapter 14.

The IRB's written procedures should describe, among other things, the scope of the unanticipated problems involving risks to subjects or others that are to be reported to the IRB, the institution, and FDA (21 CFR 56.108(b)(1)). Some IRBs interpret 21 CFR 56.108(b)(1) to mean that the IRB must receive and review all reports of unanticipated problems involving risks to human subjects or others, including those individual reports of problems occurring external to the study site for which the IRB is responsible. In practice, this can result in IRBs receiving an overabundance of adverse event reports, hiding those that are potentially significant. Currently, FDA is considering possible changes that would enhance the quality of information received by the IRB and others.

scope of the unanticipated problems

Researcher Responsibilities. Researchers must promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others (21 CFR §312.66). For drug studies, they

must promptly (immediately if it is deemed alarming) report any adverse effects that can reasonably be assumed to have been caused by the drug to the sponsor in the form of Safety Reports (21 CFR §312.64(b)). For medical devices, researchers must report any unanticipated adverse device effects to the sponsor and IRB as soon as possible (21 CFR §812.150(a)(1)). (For more information, see Chapter 14.)

Sponsor Responsibilities. The sponsor is responsible for monitoring the progress of all clinical investigations being conducted under its IND (21 CFR §312.56(a)). In drug studies, the sponsor must keep other researchers informed of new observations discovered by, or reported to, the sponsor of the drug, particularly with respect to adverse events and safe use (21 CFR §312.55(b)). They must report to the other researchers and FDA:

- any adverse experience associated with the use of the drug that is both serious and unexpected;
- any findings from tests in laboratory animals suggesting a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity; and
- in each written IND Safety Report, they must identify all the Safety Reports filed with the IND concerning similar adverse events and analyze the significance of the adverse event in light of the previous, similar reports.

Sponsors must evaluate the adverse event by promptly reviewing all information relevant to the safety of the drug from any source. (For more information on IND safety reports, see 21 CFR §312.32(c).)

A sponsor who discovers an unanticipated adverse device event must evaluate it immediately and is responsible for reporting the results to FDA and all reviewing IRBs and participating investigators within 10 working days (21 CFR §812.150(b)(1)).

Additional Safeguards for Children in Clinical Investigations (21 CFR Part 50, Subpart D)

In 2001, FDA issued an interim rule to provide additional safeguards for children enrolled in studies of FDA-regulated products (21 CFR Part 50, Subpart D) (DHHS 2001). This regulation brought FDA into compliance with provisions of the

Children's Health Act of 2000

Children's Health Act of 2000, which required that all research supported, conducted, or regulated by the Department of Health and Human Services (DHHS) be in compliance with DHHS regulations providing additional

protections for children involved as research subjects. FDA also believed that this interim rule was necessary because of expected increases in the enrollment of children in clinical studies as a result of recent pediatric initiatives. These initiatives include FDA's 1998 pediatric rule and the pediatric provisions of the Food and Drug Administration Modernization Act of 1997.

Food and Drug Administration Modernization Act of 1997

FDA adopted the provisions of the DHHS Subpart D regulations, as directed by Congress, with only those changes necessary due to differences between FDA's and DHHS's regulatory authority. FDA was aware that dissimilar or inconsistent federal requirements governing pediatric protections could be burdensome to institutions, IRBs, and the process of clinical investigations.

Consistent with the congressional directive that the Subpart D regulations must be extended to all research regulated by FDA and involving children, studies in children in support of infant formulas and in support of premarket notification of dietary supplements that contain new dietary ingredients are also subject to 21 CFR Parts 50 and 56. For information on these Subpart D regulations and the responsibilities of IRBs to protect children in research in various types of clinical investigations, see Chapter 21.

C. Exceptions from the Requirements for IRB Review and Informed Consent

IRB Review Exemption

Prior IRB review and approval is required by FDA for the use of test articles, except in cases of emergency use⁶ in life-threatening situations. The IRB exemption allows for one emergency use, provided that the IRB is notified within five business days.

emergency use in life-threatening situations

Any subsequent use must first receive IRB review and approval (21 CFR §56.104(c)). The IRB should then review the clinical investigator's report to assure that the emergency use provision was properly followed. If a second patient requires an emergency use of the same test article, FDA may exercise its enforcement discretion, recognizing the importance of trying to prevent this second person from dying. At that point, however, the IRB should implement a protocol for future uses to avoid using this emergency exemption again.

⁶ FDA regulations define emergency use as the use of a test article (e.g., an investigational drug, biological product, or medical device) on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)).

Some sponsors will not ship test articles without an IRB approval letter. In situations where the IRB cannot convene a quorum in the time available, the IRB may send a letter to the sponsor stating that the IRB is aware of the proposed use and considers it to meet all the requirements of FDA regulations. This is frequently acceptable to the sponsors and can allow them to ship the test articles. For more information on the IRB exemption, see 21 CFR §56.104.

Informed Consent Exceptions

No investigator may involve a human being as a subject in research covered by FDA regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The subject must be given sufficient opportunity to consider whether or not to participate and must be free from the possibility of coercion (21 CFR §50.20).

FDA regulations do not contain the informed consent waiver provisions in the Common Rule. Instead, FDA regulations contain three exceptions to the requirement for informed consent, if it is:

**three exceptions
to the requirement
for informed
consent**

1. necessitated by a life-threatening situation,
2. authorized by the President for a member of the armed services, or
3. for emergency research.

If there is a life-threatening situation, 21 CFR §50.23 states that the clinical investigator can administer the test article without informed consent if the investigator and an independent physician certify the following in writing:

- the human subject is confronted by a life-threatening situation necessitating the use of the test article
- informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject
- time is not sufficient to obtain consent from the subject's legally authorized representative
- there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject

If time prevents an outside physician from certifying that informed consent cannot be obtained prior to the administration of the test article, the clinical investigator's decision must be reviewed in writing by an independent physician within five business days and the IRB must be contacted and informed (21 CFR §50.23).

A presidential waiver of informed consent for a member of the armed services must be in connection with the member's participation in a particular military operation.

Furthermore, informed consent may be waived only if the President has determined in writing that informed consent is not feasible, contrary to the best interests of the military member, or contrary to the interests of national security (21 CFR §50.23(d)(1)). For a waiver of informed consent, the Secretary of Defense must certify and document to the President that:

- The extent and strength of evidence of the safety and effectiveness of the IND in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND
- The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness
- There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the IND
- Conditioning use of the IND on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission
- A duly constituted IRB has reviewed and approved the IND protocol and the administration of the investigational new drug without informed consent (21 CFR §50.23(d)(1)(i-v))

For more information on the procedures for waiving informed consent in the armed services, see 21 CFR §50.23(d).

Exception from Informed Consent for Emergency Research Under 21 CFR §50.24

Much of what have become standard, accepted medical therapies for use in acute or resuscitation clinical care have not been evaluated by adequate trials that demonstrate either safety or effectiveness. Controlled clinical trials have demonstrated that some therapies that have become standard medical practice are ineffective or even harmful. Other standard therapies, although shown to be effective in clinical trials, have significant limitations; for example, they only work in a small percentage of those individuals who receive the therapies. This means that testing of improved or additional therapies remains critically important.

Most therapeutic intervention in acute care and emergency research must be initiated immediately for life-saving purposes. For victims of heart attacks or head injuries, for example, this intervention often must be instituted in the field prior to hospital admission, when the individual is usually found to be unresponsive and unable to communicate and where there is usually no legally authorized representative of the subject available to give consent for the individual.

In 1993, FDA became aware that certain IRBs were approving research involving interventions in acutely life-threatening situations by using a “deferred consent” procedure. This term was used to describe a procedure whereby subjects or representatives of subjects are informed, after the fact, that the subject unknowingly participated in a clinical investigation of an experimental product and was administered a test article in the course of the investigation. Subjects or their representatives were then asked to ratify that participation retroactively and to agree to continuing participation.

In August 1993, the National Institutes of Health’s (NIH’s) Office for Protection from Research Risks⁷ issued letters to IRB chairpersons at various institutions having written assurances of compliance with DHHS regulations in which NIH reiterated the requirement for obtaining legally effective informed consent before enrolling subjects in a study. NIH also reminded the IRBs that the only deviation allowed by the DHHS regulations is contained in 45 CFR 46.116(d), its waiver provision. The letter stated that “deferred consent” failed to constitute informed consent under DHHS regulations.

In the summer of 1993, FDA received a number of letters from members of the neurology and emergency medicine communities expressing their concern about their ability to conduct controlled research in subjects unable to provide informed consent if FDA did not permit implied or deferred consent. FDA responded to these letters and, consistent with the conclusions reached by NIH, informed the IRBs that deferred consent does not meet the requirements of FDA regulations and does not constitute valid informed consent.

In January 1995, FDA and NIH convened the Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, where participants discussed the need to protect research subjects while allowing clinical research in the area of emergency medicine to go forward. Participants noted that, without validation of standard treatment, many patients were essentially participants in uncontrolled experiments when they received emergency care. Unfortunately, such experiments do not yield data on which rational medical decisionmaking can be based. Participants recommended that DHHS and FDA revise their regulations so that they are clear and consistent and that DHHS and FDA develop a new section in the regulations to clearly permit the waiver of informed consent for acute care research if certain defined conditions and safeguards are met.

In 1995 FDA proposed and in 1996 issued such regulations and conforming amendments⁸ to provide a narrow exception to the requirement to obtain informed consent from each subject, or the subject’s legally authorized representative, prior to enrollment in a clinical investigation. On the same date in 1996, the Secretary of DHHS published a secretarial waiver of the informed consent requirements under the DHHS regulations for studies meeting the criteria in FDA’s rule.

Requirements. The exception applies to emergency research:

1. for which an IND or IDE is in effect;
2. involving human subjects who cannot give informed consent because of their emergent, life-threatening medical condition for which available treatments are unproven or unsatisfactory; and
3. where the intervention must be administered before informed consent from the subjects’ legally authorized representative is feasible. Studies involving an exception from informed consent requirements may proceed only after a sponsor has received prior written permission from FDA and the IRB has found and documented that specific conditions have been met.

In addition, participation in the research must hold out the prospect of direct benefit to the subjects because:

- they are facing a life-threatening situation that necessitates intervention;
- evidence from appropriate animal and other preclinical studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
- risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subject and the risk and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

The regulations for emergency research contain additional specific human subjects protection requirements beyond those found in 21 CFR Parts 50 and 56 and the requirements pertaining to all IND and IDE clinical studies. These include specific requirements that (1) representatives of the community or communities in which the research will take place and from which the subjects will be drawn will be consulted about the study; (2) information about a study will be publicly disclosed before the study may proceed; and (3) the sponsor will submit a separate IND or IDE⁹ that clearly states that the protocol may include subjects who are unable

⁷ The Office for Protection from Research Risks was transferred from an agency within the Public Health Service (NIH) to the office of the secretary of DHHS in June 2000, and the name was changed to the Office for Human Research Protections.

⁸ 21 CFR 50.24 and 21 CFR Parts 56, 312, 314, 601, 812, and 814, respectively.

to consent. These additional requirements are necessary because the emergency research permitted under 21 CFR §50.24 involves a particularly vulnerable population: persons with life-threatening conditions who can neither give informed consent nor actively refuse enrollment. This lack of autonomy creates a special need for FDA, sponsors, IRBs, and clinical investigators to work closely together to protect the interests of this vulnerable population of subjects.

IRBs, in particular, have additional duties with respect to these studies. The FDA regulations at 21 CFR §50.24(a)(1-6) specify that the IRB must find and document that:

- the subjects are in a life-threatening situation for which available treatments are unproven or unsatisfactory and the collection of valid scientific information is necessary to determine the safety and effectiveness of the particular intervention
- obtaining informed consent is not feasible because the subjects will not be able to give their consent as a result of their medical condition
- the intervention under study must be administered before consent from the subject's legally authorized representative is feasible
- there is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the clinical investigation
- participation in the research holds out the prospect of direct benefit to the subjects
- the clinical investigation could not practicably be carried out without the waiver
- the proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence and specifies that the clinical investigator has committed to attempt to contact a legally authorized representative for each subject within that window, and, if feasible, ask the legally authorized representative for consent, rather than proceed without consent
- the IRB has reviewed and approved informed consent procedures and an informed consent document to be used with subjects or their legally authorized representatives in situations in which the use of such procedures and documents is feasible
- the IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation

Furthermore, 21 CFR §50.24(a)(7)(i-v) provides additional protections for the study subjects, including requirements for:

- consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn
- public disclosure prior to the investigation to the communities in which the clinical investigation will be conducted and from which subjects will be drawn of plans for the investigation and its risks and expected benefits
- public disclosure of sufficient information following completion of the clinical investigation to apprise the community and other researchers about the study, including the demographic characteristics of the research population and its results
- the establishment of an independent Data Monitoring Committee to exercise oversight of the clinical investigation
- the contacting of alternate family members if obtaining informed consent is not feasible from either the subject or a legally authorized representative and asking whether he/she objects to the subject's participation in the clinical investigation¹⁰

D. Financial Interests

Certain specific financial interests in research, if they are not managed, eliminated, or disclosed, can affect the reliability and integrity of data or the rights and welfare of subjects.

Financial Disclosure by Clinical Investigators

FDA's financial disclosure regulations (21 CFR Part 54) require any applicant who submits a marketing application of any drug, biologic, or medical device to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the regulations. These regulations are intended to ensure that any financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA are identified and disclosed by the applicant.

The regulations require applicants to certify to the absence of certain financial interests of clinical investigators or to disclose them.¹¹ If the applicant does not include certification and/or disclosure or does not certify that it was not possible to obtain the information, FDA may refuse to accept the application.

⁹ Sponsors should contact FDA if they have questions regarding whether an IND or IDE is needed.

¹⁰ FDA has issued more detailed guidance on this topic, which may be viewed at www.fda.gov/oc/gcp/guidance.html. Also see www.fda.gov/oc/gcp/regulations.html.

The types of financial arrangements that clinical investigators should disclose include the following:

- compensation made to the investigator in which the value of compensation could be affected by study outcome
- a proprietary interest in the tested product including but not limited to a patent, trademark, copyright, or licensing agreement
- any equity interest in the sponsor of a covered study—that is, any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices
- any equity interest in a publicly held company that exceeds \$50,000 in value. The requirement applies to interests held during the time the clinical investigator is carrying out the study and for one year following completion of the study
- significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigators' institution to support activities of the investigators exclusive of the costs of conducting the clinical study or other clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation or honoraria) during the time the clinical investigators are carrying out the study and for one year following completion of the study

Financial Relationships and Interests in Research

On May 12, 2004, DHHS issued a guidance document for IRBs, investigators, research institutions, and other interested parties entitled *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection* (DHHS 2004). The guidance affects FDA-regulated research because it recommends the consideration of approaches and methods for dealing with issues of financial interests under the DHHS and FDA human research subjects protection regulations 45 CFR Part 46 and 21 CFR Parts 50 and 56. The guidance expressly does not address regulatory requirements designed to enhance data integrity in research that are found in 21 CFR Part 54. The DHHS guidance document is described in Chapter 22.

E. IND Application

Current federal law requires a drug to be the subject of an approved marketing application before it is transported or distributed across state lines.

Because a sponsor will probably want to ship the investigational drug to clinical investigators in many

**approved
marketing
application**

states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine whether the product is reasonably safe for initial use in humans and whether the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three types of INDs:

1. An Investigator IND is submitted by a physician who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit an Investigator IND to propose studying an unapproved drug or an approved product for a new indication or in a new patient population.
2. An Emergency Use IND allows FDA to authorize the use of an experimental drug in an emergency that does not allow time for submission of an IND in accordance with 21 CFR §312.23 or §312.34. It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.
3. A Treatment IND is submitted for experimental drugs that show promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

¹¹ Form FDA-3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or Form FDA-3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) are available at www.fda.gov/opacom/morechoices/fdaforms/FDA-3454.pdf and www.fda.gov/opacom/morechoices/fdaforms/FDA-3455.pdf, respectively.

The IND application must contain information in three broad areas:

1. **Animal Pharmacology and Toxicology Studies:**
Preclinical data to permit an assessment regarding whether the product is reasonably safe for initial testing in humans. Also included is any previous experience with the drug in humans (often foreign use).
2. **Manufacturing Information:** Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
3. **Clinical Protocols and Investigator Information:**
Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators—professionals (generally physicians) who oversee the administration of the experimental compound—to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, obtain review of the study by an IRB, and adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be exposed to unreasonable risk.

Phases of Clinical Investigation

Clinical investigations are conducted in several phases. Phase 1 trials are designed to determine the metabolism and pharmacologic actions of a drug in humans and the side effects associated with increasing doses and, if possible, to gain early evidence on effectiveness. In phase 2, controlled clinical studies are conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 3 trials are performed after preliminary evidence suggests the effectiveness of the drug. They are intended to gather the additional information about efficacy and safety that is needed to evaluate the overall risk-benefit relationship of the drug and to provide an adequate basis for physician labeling. (For more information, see 21 CFR §312.21.)

Lawfully Marketed Drugs and Biologics

The clinical investigation of a drug or biologic that is lawfully marketed in the United States is exempt from the requirements for submission of an IND when the investigation:

- is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- is not intended to support a significant change in advertising in the case of a lawfully marketed prescription drug product;
- does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- is conducted in compliance with the requirements for IRB review set forth in 21 CFR Part 56 and with the requirements for informed consent set forth in 21 CFR Part 50;
- is conducted in compliance with the requirements of 21 CFR §312.7 (21 CFR §312.2(b)(1)).

Even if a drug or biologic is on the market, certain studies will still require an IND, and even in instances where a drug or biologic is exempt, IRB review and informed consent are always required unless the research is separately exempt in the situations discussed earlier. If a study involving an investigational new drug is presented to an IRB for review and there is no IND number identified, it is reasonable for the IRB to ask the clinical investigator to document its exempt status or explain why the study should be exempt from the IND requirements. If the IRB continues to have questions, it may contact FDA.

Drug Study Designs

An IRB is responsible for ensuring, among other things, that risks to subjects are reasonably consistent with sound research design. This section describes study designs and controls that may be presented to an IRB for its review and approval.

Before a sponsor can market a new drug or biologic, FDA must conclude that the sponsor has shown, through adequate and well-controlled clinical studies, that it is safe and effective. A well-controlled study is one in which outcomes of subjects treated with the new agent are compared with those of a suitable control population. Only well-controlled studies can reliably determine the effect of the new

safety and effectiveness shown in adequate and well-controlled clinical studies

agent and distinguish it from other influences, such as spontaneous changes, placebo effects, concomitant therapy, or observer expectations.

FDA regulations (21 CFR §314.126) cite five different kinds of controls, which can be useful in particular circumstances:

- placebo concurrent control
- dose-comparison concurrent control
- no treatment concurrent control
- active treatment concurrent control
- historical control

FDA does not express a preference for any one type of control, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that interpretation of historically controlled studies is often problematic. This is because it is generally difficult to determine whether historical control groups are comparable to the treated subjects in terms of variables that could affect outcome; in most cases, there are many reasons why these groups would be different. Thus, researchers reserve the use of historical control studies for special circumstances—where the disease treated has high and predictable mortality (a large difference from this usual course would be easy to detect) and where the effect is self-evident (e.g., a general anesthetic). Even in these cases, however, concurrent controls may be needed for adequate assessment of product safety.

Placebo control, no treatment control (suitable when the researcher believes that objective measurements make blinding unnecessary), and dose-comparison studies are all study designs in which one intends to show a difference between the test article and some control. Studies using an active treatment concurrent control, on the other hand, frequently intend to show that there is little or no difference between the test article and the recognized effective agent (active control) and thereby demonstrate the effectiveness of the new agent. Such trials are often called “equivalence” or “noninferiority” trials. In some circumstances this is a fully valid design that can produce readily interpretable results; for example, one generally uses active controls in antibiotic trials because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. Often, however, the active control design is inadequate to support any conclusion about the effectiveness of the test article.

When the purpose of an active control trial is to show that the new agent is more effective than the active control, its interpretation is straightforward; however, when the purpose is to demonstrate effectiveness by showing equivalence/noninferiority, difficulties arise because showing no difference between the new agent and the active control does not

necessarily establish the effectiveness of the new agent. In many disease areas, trial results are highly variable, and known effective agents often fail to appear superior to the placebo in clinical trials. Without a placebo group, a finding of no difference in an active control study could mean that both agents were effective, but it could also mean that neither agent was effective in that study. For certain types of drugs, such as analgesics, antidepressants, or anti-anxiety drugs, failure to show superiority to the placebo in a given study is common. Active control trials are similarly problematic in studies of new antihypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these cases, active control trials that show no difference between the new drug and control are of little value as primary evidence of effectiveness.

Another problem with active control equivalence/noninferiority studies is that they do not provide the same incentives toward study excellence as trials intended to show a difference between treatments. Poor quality of study conduct—for example, poorly defined diagnostic criteria, inaccuracies in measurement, or poor compliance with the study protocol—often dilutes the observable difference between treatments. When the intent of the study is to demonstrate the superiority of the new agent to a placebo or an active control, the investigators have a major incentive to minimize errors in study conduct, as these are likely to make it more difficult to show differences between treatment arms. When the intent of the study is to show no difference between treatments, the incentives for study quality are reduced.

Deciding whether an active control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment that is influenced by the available evidence. For example, if one examines prior studies of a proposed active control and finds that one can almost always distinguish the test article from the placebo in a particular setting (subject population, dose, and other defined parameters), an active control design may be reasonable if conducted in that setting.

It is often possible to design a successful placebo-controlled trial that does not raise ethical issues. Treatment periods can be kept as short as necessary to establish a treatment effect, and early escape mechanisms can be built into the study so that subjects will not undergo prolonged placebo treatment if they are not doing well. Randomized placebo-controlled therapy withdrawal studies can minimize exposure to placebo or unsuccessful therapy. In such studies, one can randomly assign apparent responders to a treatment in an open study to continued treatment or to the placebo and quickly remove subjects who fail (e.g., when blood pressure rises or angina worsens), with such failure representing a study endpoint.

IRBs may face difficult issues in determining the acceptability of placebo-controlled and active control trials. Placebo-controlled trials, **placebo-controlled and active control trials** regardless of any advantages in the interpretation of results, are almost never ethically acceptable where existing treatment is life prolonging or prevents serious irreversible morbidity. Exceptions might be cases in which the side effects of the treatment are so extreme that many individuals refuse the standard therapy despite its known benefits. However, it is critical to review the evidence that permanent harm would result from denial of active treatment. Because alternative study designs, especially active control studies, may not be informative—exposing subjects to risk without being able to collect useful information—their justification should be carefully considered before they are approved.

Emergency Use of an Investigational Drug or Biologic

In an emergency, a patient may require an investigational drug or biologic when there is not enough time to submit an IND. These situations are usually serious, but not necessarily life threatening. The first step for the physician is to determine whether there is an existing study protocol under IND with the manufacturer and whether the patient meets the entrance criteria. This could be a treatment protocol or an open label protocol.

A treatment protocol under 21 CFR §312.34(b) requires that:

- the drug is intended to treat a serious or immediately life-threatening disease
- there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population
- the drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed
- the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence

An existing open label protocol is less controlled and usually carried out to obtain added safety data. It is established, in part, to allow for the subjects and controls in a study to continue receiving the drug or biologic prior to marketing approval from FDA. IRB review and informed consent are still required.

If the patient meets the entrance criteria for either study protocol, the physician requests the drug or biologic for emergency use from the manufacturer. If the patient does not meet the criteria, or if there is no protocol for which the

patient is eligible, the physician will file for an emergency use IND. If the manufacturer agrees to provide the drug or biologic, FDA must be contacted and assured that IRB review and informed consent will be obtained, unless the situation qualifies for an exception under 21 CFR §56.104, 21 CFR §56.102(c), or 21 CFR §50.23. For more information, see 21 CFR §56.104(c), 21 CFR §56.102(d), and 21 CFR §50.23.

A request for emergency use authorization may be transmitted to FDA by telephone or other means of rapid communication.¹² Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization (21 CFR §312.36).

Radioactive Drugs Used in Research

In reviewing studies involving radioactive drugs, IRBs should understand when an IND is required and when a study can instead be reviewed by a Radioactive Drugs Research Committee (RDRC). The purpose of the research study determines whether IND regulations (21 CFR Part 312) or regulations for *Radioactive Drugs for Certain Research Uses* (21 CFR §361.1) apply.

**Radioactive Drugs
Research
Committee (RDRC)**

An IND is required when the purpose of the study is to determine the safety and efficacy of the drug or for immediate therapeutic, diagnostic, or similar purposes. If an IND is in effect for a radioactive research drug, then the investigational drug is subject to the IND regulations (21 CFR Part 312), rather than the regulations at 21 CFR §361.1.

Under 21 CFR §361.1, radioactive drugs, as defined in 21 CFR §310.3(n), may be administered to human research subjects without obtaining an IND when the purpose of the research project is to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry. Certain basic research studies, for example, studies to determine whether a drug localizes in a particular organ or fluid space or studies to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of 21 CFR §361.1. Such basic research studies must be conducted under the conditions set forth in 21 CFR §361.1(b), which include a limit on the radiation dose as specified in 21 CFR §361.1(b)(3), a limit on the pharmacologic dose such that the dose does not cause a clinically detectable pharmacological effect, and approval by an RDRC.

¹² 21 CFR 312.36 was amended effective April 6, 2004, to update the FDA contact information for emergency use INDs. See www.fda.gov/cber/rules/emerguseind.htm.

An RDRC must obtain and maintain approval by FDA as outlined in 21 CFR §361.1(c). RDRCs must register with the Division of Medical Imaging and Radiopharmaceutical Drug Products, (HFD-160), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, Maryland 20857.

All RDRC-approved studies must also be approved by an IRB prior to initiation (21 CFR §361.1(d)(9)). Informed consent must be obtained from the research subjects (21 CFR §361.1(d)(5)).

F. Investigational Device Exemption

In reviewing research involving medical devices, IRBs should know when an approved IDE is needed.

Lawfully Marketed Medical Devices

The clinical investigation of a lawfully marketed medical device does not require an additional IDE when:

- the device was in commercial distribution immediately before May 28, 1976, and used or investigated in accordance with the indications in labeling in effect at that time;
- the device was introduced on or after May 28, 1976, and FDA has determined it to be substantially equivalent to a medical device in commercial distribution immediately before May 28, 1976;
- the device is diagnostic and the testing is
 - noninvasive
 - does not require an invasive sampling procedure that presents significant risk,
 - does not by design or intention introduce energy into a subject
 - is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure
- the device is undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more medical devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk (21 CFR §812.2(c)).

Although a lawfully marketed medical device may not require an IDE, studies are still required to comply with IRB review and informed consent regulations (see 21 CFR Parts 56 and 50, respectively).

Significant Risk and Nonsignificant Risk Medical Device Studies

For medical device studies, FDA regulations place additional review responsibilities on IRBs based on the type of risk associated with the study. There are two types of medical device studies: significant risk (SR) and nonsignificant risk (NSR). The regulations at 21 CFR §812.3(m) define an SR study as the study of an investigational medical device that:

- is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and presents a potential for serious risk to the health, safety, or welfare of a subject;
- otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An NSR medical device study is one that does not meet the definition above. Both types of studies require IRB review and informed consent, although SR studies are more thoroughly regulated.

SR medical device studies must follow all of the IDE regulations contained in 21 CFR Part 812 and must have an IDE application approved by FDA. NSR medical device studies, on the other hand, are only required to abide by 21 CFR §812.2(b) and are not required to have an IDE application. An NSR medical device study may begin as soon as the IRB approves it, and no progress or final reports need to be sent to FDA. These studies can go on without FDA knowledge or approval if the IRB agrees with the sponsor that the study is NSR.

The sponsor of the medical device study is responsible for determining whether it is SR or NSR and for justifying its decision. The sponsor is encouraged to keep the IRB informed of what, if anything, FDA says about the medical device, as well as of any thoughts from other IRBs. If the sponsor determines that the device study is SR, it must file an IDE application with FDA and advise the clinical investigators of its status. FDA is responsible for the final decision; if FDA determines that a medical device study is SR after it has already begun, it will inform the sponsor and require an IDE application before it can continue. If FDA has already received an application because the sponsor determined that it was

SR and FDA disagrees, FDA will notify the sponsor in writing, who then forwards the notification to the IRB as an NSR study.

It is not necessary for an IRB to make a risk determination if the medical device study is exempt from the requirements of the IDE regulations or if the medical device study already has an approved IDE. An approved IDE would indicate that the sponsor and FDA have already determined that it is an SR study; however, if the study is not exempt or does not have an IDE, the IRB should:

- have standard operating procedures that explain how NSR determinations are made;
- review relevant information when making SR and NSR determinations;
- review an NSR study using the criteria at 21 CFR §56.111 or defer a decision on the protocol and inform the clinical investigator and/or sponsor if it believes the classification of the NSR medical device study should be SR;
- require proof of an approved IDE application for the medical device at FDA if it chooses;
- document its SR or NSR determination in the IRB minutes.

The IRB should consider several factors when making an SR and NSR determination, including:

- the basis for the risk determination;
- the nature of harm that may result from use of the medical device; and
- whether or not the subject will need to undergo a procedure, especially a surgical one, as part of the investigational study and the potential harm of that procedure and any medical device implanted in the subject.

IRBs should not confuse their responsibility to review and approve research for implementation at a clinical site with the SR and NSR determination. IRBs make the SR or NSR determination before the IRB conducts its review of the study under 21 CFR Part 56. The judgment about whether a study poses an SR or NSR is based solely on the significance of the potential harm that may result from the use of the medical device, while the IRB's decision to approve a study for implementation is based on the study's risk-benefit assessment. Furthermore, the IRB should not confuse NSR with minimal risk. Minimal risk is used, in part, to determine if a medical device study is eligible for an expedited review procedure and is unrelated to the SR or NSR determination.

Emergency Use of an Investigational Medical Device

Procedures governing the emergency use of an investigational medical device are covered in two separate documents: the IDE regulation (21 CFR Part 812) and FDA's *Guidance for the Emergency Use of Unapproved Medical Devices*, (hereinafter referred to as the *Emergency Use Guidance*) (FDA 1985).

**Guidance for the
Emergency Use of
Unapproved
Medical Devices**

The IDE regulation recognizes that emergencies may arise in which there will be a need to use an investigational medical device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Therefore, the regulation permits deviations from the investigational plan when necessary to protect the life or physical well-being of a subject in an emergency (21 CFR 812.35(a)). Prior approval for shipment or emergency use of the investigational medical device is not required, but the use should be reported to FDA by the IDE sponsor within five working days of the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed (as discussed below), and patient outcome information.

In addition to the IDE regulation, emergency use is also addressed in an FDA guidance document. FDA issued the *Emergency Use Guidance* because the IDE regulation does not address emergency use comprehensively (by not defining the term *emergency use*, identifying the patient protection measures that should be followed in such situations, or addressing the emergency use of medical devices not covered by an IDE). This guidance defines an unapproved medical device as a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under Section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e) or an approved IDE under Section 520(g) of the act (21 USC 360j(g)). As discussed in the guidance, an unapproved medical device should normally only be used in human subjects if it is approved for clinical testing under an IDE and if it is used by an investigator for the sponsor in accordance with the terms and conditions of the application. Emergency use of an unapproved medical device, however, may also occur:

- when an IDE for the device does not exist,
- when a physician wants to use the device in a way not approved under the IDE, or
- when a physician is not an investigator under the IDE.

The *Emergency Use Guidance* document was intended to address these emergency situations. As stipulated in the guidance, a physician who intends to treat a patient with an unapproved medical device in an emergency should conclude that:

- the patient has a life-threatening condition that needs immediate treatment;¹³
- no generally acceptable alternative treatment for the condition exists; and
- because of the immediate need to use the medical device, there is no time to use existing procedures in order to obtain FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved medical device, and to have substantial reason to believe that benefits will exist. In the event that a medical device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

- informed consent from the patient or a legal representative;
- clearance from the institution as specified by its policies;
- concurrence of the IRB chairperson;
- an independent assessment from an uninvolved physician; and
- authorization from the IDE sponsor, if an approved IDE exists for the medical device.

Although it is not provided for under this guidance, a physician who is faced with an emergency such as described above will often contact FDA to discuss his/her patient's condition. In this situation, the Office of Device Evaluation (ODE) acts in an advisory role, rather than in an approving role. The ODE employee who receives the call should discuss the emergency use criteria with the physician, but the responsibility for making the decision regarding whether the situation meets the emergency use criteria and whether the unapproved medical device should be used lies with the physician. If the physician decides to proceed with the emergency use of the medical device, the ODE employee should advise the physician of the above patient protection procedures to be followed before the emergency use occurs and should fill out the Emergency Use Checklist. This checklist helps to ensure that the criteria for emergency use have been met and that the physician has

Emergency Use Checklist

been informed that he/she is expected to follow as many patient protection procedures as possible. After discussing the situation with the physician and completing the checklist, it should be filed in the Emergency Use Report File. After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the medical device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. If no IDE exists, the physician should submit a follow-up report on the use of the medical device to the IDE sponsor staff. This report should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.

G. FDA Inspection of Biomedical Research

Under the agency's Bioresearch Monitoring (BIMO) Program, FDA conducts inspections of sponsors, monitors, CROs, clinical investigators, IRBs, and bioequivalence facilities. When a marketing application is submitted to the agency, the BIMO Program of the Center¹⁴ with jurisdiction over the product selects several clinical study sites and issues assignments to FDA's field offices to inspect the sites. The Center may also issue assignments to inspect the sponsor, the IRB, the monitor, or a CRO related to the study. The purpose of these inspections is:

- to verify the integrity of the data submitted to the agency;
- to protect the rights and welfare of the study subjects; and
- to determine whether the clinical investigator or sponsor, or IRB or other facility, complied with FDA's regulations for the conduct of the study. FDA inspects about 250 to 300 IRBs each year as part of its routine surveillance program.

During an IRB inspection, the FDA inspector will review the IRB's roster and the minutes of the IRB's meetings to determine whether they provide sufficient detail to show the attendance at the meetings, actions taken, the specifics of who voted and how, the basis for requiring changes in research, and a written summary of controverted issues and their resolutions.

FDA inspector

The following is an example of the typical questions that an FDA inspector might try to resolve or answer during an

¹³ As a matter of practice, for circumstances covered by this guidance document only, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions, as well as other situations involving risk of irreversible morbidity. This is consistent with the FDA Modernization Act.

¹⁴ FDA's five Centers (the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, the Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine) and the Office of Regulatory Affairs jointly administer and coordinate inspection policy for the BIMO Program.

inspection of an IRB. Although not exhaustive, these questions provide a sense of the scope of FDA's IRB inspections:

- does the IRB have and follow written procedures for the initial and continuing review of research?
- Were a majority of IRB members present at all meetings during which research studies were reviewed and approved?
- did any IRB member participate in initial or continuing review of any project in which the member had a conflict of interest (other than to provide information requested by the IRB)?
- does the IRB maintain (and regularly update) its list of IRB members, identified by name, earned degree, representative capacity, and indications of experience (board certifications and licenses) sufficient to describe each member's chief anticipated contributions to the IRB deliberations and his/her relationship to the institution?
- did the IRB notify the institution, the clinical investigator, and FDA regarding any terminations or suspensions of approval of research?
- do the IRB's procedures address how to determine whether an investigation involves an SR or NSR medical device?

If there is a related inspection of a study conducted by a clinical investigator at the site, the FDA inspector might also review the IRB's activities with respect to the IRB's review of that study and its informed consent document. For example:

- did the clinical investigator obtain IRB review and approval for the study?
- was IRB approval obtained before he/she began enrolling subjects into the study?
- did the IRB approved consent form include all of the basic elements of consent found in 21 CFR §50.25?
- did the clinical investigator use the correct version of the consent form (the version that was approved by the IRB), including any later amendments?

At the end of an inspection, the FDA inspector conducts an exit interview. During this interview, the inspector dis-

cusses the findings from the inspection and may issue a written Form FDA-483 (Inspectional Observations).¹⁵ Following the inspection, the FDA inspector prepares a written report and sends it to headquarters for evaluation. After FDA headquarters reviews the report, it usually issues a letter to the IRB. The letter is one of the three following types:

1. A letter that generally states that FDA observed no significant deviations from the regulations—this letter does not require any response from the clinical investigator.
2. An informational letter that identifies deviations from regulations and good clinical practices—this letter may request a response from the clinical investigator. If FDA requests a response, the letter will describe what is necessary and provide the name of a contact person for questions.
3. A warning letter (WL) that identifies violations of the regulations that require prompt correction by the clinical investigator—this letter requires a formal written response to **Warning Letter** FDA and will provide the name of an FDA center person as a contact for questions. In these cases, FDA may inform both the study sponsor and the reviewing IRB of the deficiencies. FDA may also tell the sponsor whether the clinical investigator's procedural deficiencies suggest ineffective monitoring by the sponsor.

If an IRB or other inspected party receives a WL, it has 15 days to respond in writing and provide an explanation of the action that will be taken to correct the violations. Failure to respond to the letter may result in regulatory action, up to and including disqualification of the IRB.

For more detailed information about the procedures that FDA investigators use, readers are invited to review the *Compliance Program Guidance Manual* chapters pertaining to bioresearch monitoring inspections.¹⁶ In addition, FDA inspections, findings, and sanctions are discussed in Chapter 6 of this resource manual.

¹⁵ This form is available at www.fda.gov/opacom/morechoices/fdaforms/FDA-483.pdf.

¹⁶ Available at www.fda.gov/ora/compliance_ref/bimo/default.htm. Previously issued WLs may be viewed on FDA's good clinical practice Web site at www.fda.gov/oc/gcp, under the heading "Enforcement Information."

Key Concepts: FDA-Regulated Research

- FDA regulations for the protection of human subjects apply to research involving FDA-regulated products. FDA's regulations were harmonized with the Common Rule, which governs federally conducted and funded research to the extent permitted by FDA's statute and mission. When a federally funded study involves an FDA-regulated product, both FDA's regulations and the Common Rule apply.
- In addition to obtaining IRB approval, a clinical investigator is required, among other things, to
 - 1)conduct the study in accordance with the relevant, current protocol and only make changes after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
 - 2)inform any potential subjects that the test articles are being used for investigational purposes;
 - 3)ensure that the requirements for obtaining informed consent are met (21 CFR Part 50); and
 - 4)ensure that the requirements for IRB review and approval are met (21 CFR Part 56).
- A sponsor-investigator is an individual who both initiates and conducts an investigation and under whose immediate direction the test article is administered or dispensed. Sponsor-investigators must comply with the regulations that apply to both sponsors and investigators (21 CFR §312.3).
- Sponsor obligations transferred to a CRO must be described in writing, particularly if not all obligations are transferred. Any obligation that is not included in the written description is deemed not to have been transferred.
- FDA's Subpart D regulations concerning children in FDA-regulated research contain requirements comparable to those in the DHHS Subpart D regulations, with only those changes necessary due to differences between FDA's and DHHS's regulatory authority.
- FDA regulations contain three exceptions to the requirement for informed consent if it is:
 - 1)necessitated by a life-threatening situation,
 - 2)authorized by the President for a member of the armed services, or
 - 3)for emergency research.
- The regulations for emergency research contain additional specific human subjects protection requirements beyond those found elsewhere in 21 CFR Parts 50 and 56 and the requirements pertaining to all IND and IDE clinical studies. These include requirements for community consultation, disclosure, and a separate IND or IDE.
- Any applicant who submits a marketing application of any drug, biologic, or medical device is to submit certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies covered by the regulations.
- Certain studies of marketed products will require an IND. If they are exempt from IND requirements they will generally require IRB review and informed consent.
- FDA regulations (21 CFR §314.126) cite five different kinds of controls that can be useful in particular circumstances:
 - 1) placebo concurrent control;
 - 2) dose-comparison concurrent control;
 - 3) no treatment concurrent control;
 - 4) active treatment concurrent control; and
 - 5) historical control.
- A request for emergency use authorization for an investigational drug or biologic may be transmitted to FDA by telephone or other means of rapid communication. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization and informing the IRB.
- An IND is required for radioactive drugs used in research when the purpose of the study is to determine the safety and efficacy of the drug or when it is for immediate therapeutic, diagnostic, or similar purposes. If an IND is in effect for a radioactive research drug, then the investigational drug is subject to the IND regulations (21 CFR Part 312), rather than the regulations at 21 CFR §361.1.
- SR medical device studies must follow all the IDE regulations contained in 21 CFR Part 812 and have an IDE application approved by FDA. NSR medical device studies, on the other hand, are only required to abide by 21 CFR §812.2(b) and are not required to have an IDE application.

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Key Concepts: FDA-Regulated Research

- The IRB should consider several factors when making an SR and NSR determination, including
 - 1)the basis for the risk determination;
 - 2)the nature of harm that may result from use of the medical device; and
 - 3)whether or not the subject will need to undergo a procedure, especially a surgical one, as part of the investigational study and the potential harm of that procedure and any medical device implanted in the subject.
- After the emergency use of an investigational medical device, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists, the physician provides the IDE sponsor with patient follow-up information. If no IDE exists, the physician submits a follow-up report on the use of the device to the IDE sponsor staff.
- The purpose of FDA inspections under the BIMO Program is (1) to verify the integrity of the data submitted to the agency, (2) protect the rights and welfare of the study subjects, and (3) determine whether the clinical investigator or sponsor, or IRB or other facility, complied with FDA's regulations for the conduct of the study.

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Chapter 17

Social and Behavioral Research

- A. Introduction
 - B. Psychological and Social Harms
 - C. Research Involving Deception
 - D. Privacy and Confidentiality Concerns in Social and Behavioral Research
 - E. "Third Party" as Subject
 - F. Research Exemptions in Social and Behavioral Research
 - G. Expedited Institutional Review Board Review of Social and Behavioral Research
 - H. Internet Research
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References



A. Introduction

Social and behavioral research typically is designed to investigate or observe social interaction or influence, cognitive or affective processes, or behavior. As such, issues to consider in the ethical review of social and behavioral research are sometimes viewed as distinct from those pertinent to biomedical research. Moreover, the regulatory and ethical paradigms in place today (e.g., federal regulation, the *Nuremberg Code*) tend to focus on the biomedical model for research. This chapter presents issues that Institutional Review Boards (IRBs) should consider in reviewing social and behavioral research, taking into account the fact that some research methods tend to be used more often in social and behavioral research:

- surveys (e.g., self-administered questionnaires about attitudes)
- individual or group interviews (e.g., focus groups for political science research)
- individual or group observations (e.g., students in a classroom setting)
- record or database analyses (e.g., analysis of aggregated household spending data)
- experimental interventions (e.g., smoking cessation research)
- manipulation of the subject's environment (e.g., measuring response to noise)

Although harms to subjects can occur in social and behavioral studies, they tend to be nonphysical harms that require a different type of evaluation and series of considerations in assessing risk. The most important point to keep in mind when assessing social and psychological risks is that these risks are real risks and they are not any less serious because they do not involve physical harm. Developing metrics by which to evaluate risks can be challenging when potential harms include emotional distress, psychological trauma, invasion of privacy, embarrassment, loss of social status, loss of employment or other financial harm, and unwanted self-revelation, as occurred, for example, in Stanley Milgram's study of obedience to authority (1974). Psychological harms such as these can have a potentially debilitating effect on short- and long-term psychological and/or social function. Even simple surveys or interviews could result in psychological stress for certain individuals who have unresolved conflicts (e.g., involving death, physical or sexual abuse, depression or suicide, parental abandonment, or divorce). Finally, although the probability of physical harm may be small, physical harm can occur in social and behavioral research, and its risk of occurrence must be anticipated and thoroughly evaluated.

**nonphysical
harms**

B. Psychological and Social Harms

When evaluating social and behavioral science research, IRBs must carefully evaluate the probability and magnitude of all types of potential harm to subjects. IRBs must be prepared to evaluate the likelihood of subjects experiencing such harm as the result of participating in proposed research. They also must be prepared to require consideration of alternative procedures that are less risky and special safeguards—for example, preventive protections and debriefings, adequate disclosure of risks in the informed consent, and mechanisms for protecting the confidentiality and privacy of the subjects—as well as methods for dealing with harm should it occur. IRB approval should be conditioned on the existence of these safeguards if an IRB believes that harms might actually occur. IRBs that do not have the expertise to make informed determinations in this area must seek the assistance of expert consultants in evaluating the probability and magnitude of potential harm and the need for additional protections. The IRB is responsible for:

- identifying risks;
- determining that risks are minimized;
- determining that “risks to subjects are reasonable in relation to anticipated benefits;” and
- “determining that subjects are adequately informed about any reasonably foreseeable risks or discomforts” (§____.111(a)).

It is important to note that if an IRB reviews such protocols without having sufficient expertise, the IRB is not compliant with the regulations.

The IRB should require that the protocol for any research in which an intense psychological reaction is possible include criteria for halting a subject's research participation and initiating a supportive intervention. Some psychological research should be conducted only by a trained clinician who is capable of evaluating the severity of the response and intervening effectively. For other research, it is adequate to provide access to counseling should the need arise.

Informed Consent in Social and Behavioral Research

The informed consent process is very important in social/behavioral research. In addition to the regulatory requirements, the risks should be explained to subjects in terms to which they can relate, preferably those from their everyday life experiences. Because the evaluation of social and psychological risk is highly subjective, the consent process should empower subjects to make their own determinations about risk. For example, an IRB can require a self- or prescreening statement in the recruitment advertisement about the study, such as “If you have had a traumatic experience, you may not want to participate.”

C. Research Involving Deception

Deception research is a controversial but sometimes critical form of human research. Certain social and behavioral research paradigms require that subjects not be fully informed or that they be actively misled about the nature or purposes of the research or the procedures to be experienced in the research. The use of such deception can be justified only when providing full information to subjects would so confound the research that it would defeat its purpose.

IRBs reviewing research involving incomplete disclosure or outright deception must apply all relevant regulatory requirements and ethical principles, as well as common sense and sensitivity, to the review. From a regulatory standpoint, the use of deception can never be approved when the research involves greater than minimal risk to subjects or when any of the relevant criteria listed below cannot be substantiated.

From an ethical standpoint, an IRB should ensure that the principle of respect for persons is honored. In recognition of subjects' autonomy, approval of research that uses deception should be withheld if the IRB believes that the failure to provide specific information about the research would reasonably be expected to affect subjects' willingness to participate.

IRBs also must exercise common sense and sensitivity by ensuring that the ethical principles of beneficence and justice are upheld and that deception is not permitted for trivial reasons or for scientifically questionable research.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects will be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a countervailing benefit.) It might even be possible in some cases to create a consent document that informs the subject that certain aspects of the study information are being withheld at the time and that additional information may be provided later.

debriefing

Deception can be permitted only where an IRB determines that waiver of the usual informed consent requirements is justified under the criteria present at §____. 116(d). Specifically, the IRB must find and document in a protocol-specific fashion that all four of the following criteria have been satisfied:

1. The research presents no more than minimal risk to subjects.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Where appropriate, the subjects will be provided with additional pertinent information after participation.

Again, it is important to note that the Common Rule makes no provision for the use of deception in research that poses greater than minimal risk of harm to subjects.

D. Privacy and Confidentiality Concerns in Social and Behavioral Research

Restricting access to private information and the need to maintain the confidentiality of private information are important issues in social and behavioral research. As indicated in Chapter 13, the concept of privacy pertains to whether the investigator has legitimate access to private information for research purposes. Private information includes “information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public” (§____.102(f)(2)). The concept of confidentiality (discussed below) pertains to whether there are sufficient protections against unauthorized disclosure of information once it has been obtained.

The IRB’s first task in considering protection of privacy and confidentiality issues is verifying that the investigator has legitimate access to subjects’ private information *for research purposes*. Individuals who have divulged private information for a specific purpose (whether that purpose is for personal or social considerations, treatment, or research) have a right to expect that use of their information will be limited to the intended purpose. Unauthorized use of their private information constitutes at least dignitary harm, and it can easily result in significant social or psychological harm.

In general, private identifiable information may not be obtained for research purposes from private (nonpublic) records or other sources without IRB approval and the informed consent of the subject. Such is the case even for activities intended to identify potential subjects who will later be approached to participate in the research. However, there are circumstances that will allow an exemption from the regulations to be granted and circumstances under which the IRB may approve a waiver of the requirement to obtain informed consent (see §____.101(2) for exempt research and §§____.116(c) and (d) for waiver or alteration of the

informed consent requirements). Exempt research is further discussed in Chapter 10, and waiver of consent is discussed in Chapter 12.

Safeguarding Confidentiality

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that could potentially harm subjects. When information linked to individuals will be recorded as part of the research design, IRBs must ensure that adequate precautions exist to safeguard the confidentiality of the information (§____.111(a)(7); 21 CFR 56.111(a)(7)).

**individually
identifiable private
information**

Regulations require that subjects be informed of the extent to which the confidentiality of research records will be maintained (§____.116(a)(5); 21 CFR 50.25(a)(5)).¹ Pledges such as “confidentiality will be strictly maintained” or “confidentiality is assured” are misleading and impossible to fulfill. Absolute confidentiality is simply not achievable in today’s world and should not be promised.

Instead, IRBs should require in the project plan and in informed consent documents specific descriptions of the mechanisms that will be used to protect the confidentiality of information or, if applicable, of any instances in which confidentiality will not be maintained. If the investigators will comply with state mandatory reporting requirements (e.g., for reporting child abuse) or anticipate other circumstances in which confidentiality will not be preserved, informed consent must describe these situations clearly and specifically.

IRBs and subjects must be aware that the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and other federal agencies have the right to inspect research records, including consent documents and relevant clinical records of individual subjects, to ensure compliance with regulatory requirements and program standards (§____.115(b); 21 CFR 56.115(b)). Informed consent must clearly and specifically describe this federal prerogative. In addition, the IRB has the authority to inspect these records.

In studies where highly sensitive information is collected, IRBs and investigators should recognize that simple protocol references to tried-and-true protections such as removing subjects’ names from questionnaires, using simple coded identifiers, and storing data in locked filing

¹ See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html.

cabinets may not be sufficient for social and behavioral studies in which highly sensitive identifiable information is collected. At the very least, IRBs will want to obtain clarification from investigators about:

- exactly who will have access to identifiers and identifying codes
- whether subjects might be identified indirectly by matching study information to available public or nonpublic information
- the physical security arrangements in the facility and the office where information is stored
- whether online research is to be conducted and whether safeguards are in place for protecting the confidentiality of participants
- plans for destroying all identifiers as soon as feasible

IRBs should also consider security requirements for electronic storage and transmittal of data. It is becoming increasingly necessary for IRBs and investigators to seek advice from information technology experts when reviewing research involving highly sensitive information.

IRBs that review research for which maintaining the confidentiality of data is a serious issue should have at least one member (or a consultant) who is familiar with the strengths and weaknesses of the different confidentiality mechanisms available.

Some examples of confidentiality mechanisms that may be appropriate for social science research are listed below (the examples in parentheses illustrate situations in which the mechanisms may be particularly useful, but these are by no means exhaustive):

confidentiality mechanisms

- formal confidentiality training programs for research personnel (e.g., for interviewers or data entry personnel in survey research)
- formal limitations on access to sensitive information (e.g., where subjects may be known to or identifiable by research personnel)
- randomly generated coding systems (e.g., where data analysis will be performed by an external collaborator or contractor)
- data encryption (e.g., for data transmitted electronically)
- physical security (e.g., for hard copies of response sheets)
- electronic security (e.g., for electronically stored data)

Certificates of Confidentiality

A Certificate of Confidentiality is a specific device that can be used to protect confidentiality (see also Chapter 13). The Public Health Service Act §301(d), 42 USC §241(d), “Protection of privacy of individuals who are research subjects,” states:

The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.

The privacy of the research subjects referred to in §301(d) is protected through the issuance of Certificates of Confidentiality. These certificates provide protection against compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical, or other research. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation. This protection is not limited to federally supported research.

Certificates of Confidentiality are issued by the National Institutes of Health (NIH)² and other DHHS agencies to protect identifiable research information from forced or compelled disclosure. *OHRP does not issue Certificates of Confidentiality.*³

Certificates of confidentiality protect subjects from compelled disclosure of identifying information, but they do not prevent the voluntary disclosure of identifying characteristics of research subjects. Researchers, therefore, are not prevented from voluntarily disclosing certain information about research subjects, such as

compelled disclosure

² For Certificate of Confidentiality contacts at the NIH, see <http://grants.nih.gov/grants/policy/coc/contacts.htm>.

³ For more information on Certificates of Confidentiality and their limitations, see <http://grants.nih.gov/grants/policy/coc/index.htm>. See also Chapter 13 of this guide.

evidence of child abuse or a subject's threatened violence to self or others. If a researcher intends to make such voluntary disclosures, the consent form should clearly indicate this. Furthermore, Certificates of Confidentiality do not prevent other types of intentional or unintentional breaches of confidentiality. As a result, investigators and IRBs must ensure that other appropriate mechanisms and procedures are in place to protect the confidentiality of the identifiable private information to be obtained in the proposed research.

E. "Third Party" as Subject

If private, identifiable information is collected on other living individuals in addition to the primary target subjects of the research, the IRB must consider the risk of harm to those nontarget individuals as well. The IRB may require additional protections, redesign of the study, or the informed consent of nontarget individuals (unless the requirement for informed consent can be waived). The individuals who are not the direct targets of the research are sometimes referred to as "third parties" or "secondary" subjects (see also Chapter 24 on genetics research).

Some research, particularly survey research, may ask individuals to provide information about family members. This may occur, for example, when the research includes subjects who were abused during childhood, individuals with addictive disorders, or individuals participating in genetic research concerning inheritance patterns. Debate is ongoing about the status of these individuals in the system of research protections. OHRP has intervened in some cases with the opinion that such third parties are to be considered research subjects if they are identifiable (Kendler 2001). Other groups point to the difficulty of expanding human subjects protections to individuals who are not the direct subjects of research and who are not contacted by or involved with the investigator in any way.⁴

The question of when third parties are or become human subjects has been under debate for several years. Scholarly articles have been written and recommendations have been made at the national level by NIH and by an advisory committee to OHRP (the National Human Research Protections Advisory Committee [NHRPAC]). In 2001 NHRPAC wrote:

The determination of who is and is not a research subject rests with the IRB. In most instances the identity of human subjects of research is clear. Whether through interaction, intervention, or identifiable private information, persons are human subjects when they are

providing personal or contextual information about their own lives, circumstances, perceptions, or histories, even when they make reference to others.

Simply because a third party is contemplated in research design or a third party's information is recorded in research results does not necessarily suggest that a third party must be regarded as a research subject.

Investigators in designing and proposing research projects and IRBs in considering and reviewing research projects and in conducting continuing review should consider how the research design might focus not only on the identified subjects, but on other persons as well.

In cases in which a research project's design collects a significant amount of information in identified form on third parties, the investigator and IRB should consider whether any of these third parties should be regarded and treated as research subjects themselves.

In making this determination the following factors should be considered among others:

- (1) the quantity of information collected on the third party
- (2) the nature of information collected
- (3) the sensitivity of the information collected and the possibility that information may be turned to possible harm to the third party; and
- (4) the possibility of recording information on third parties in such a way as to protect the identity of those parties⁵

In 2001 NIH also issued a statement on third-party subjects⁶ in which it concluded that "third parties are not human subjects per se. They may become human subjects in the course of a research study if private, readily identifiable information about them is obtained by the researcher."

OHRP is in the process of drafting guidance to clarify how the regulations should be interpreted on this point. The guidance will take account of all the perspectives and recommendations that have been put forward on this issue and will be disseminated for public comment.

⁴ See www.nih.gov/sigs/bioethics/nih_third_party_rec.html.

⁵ See www.hhs.gov/ohrp/nhrpac/mtg01-02/third.pdf.

⁶ See www.nih.gov/sigs/bioethics/nih_third_party_rec.html.

Table 17.1**Research Exempt from the Common Rule at §____.101(b)⁷**

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices such as research on regular and special education instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures,* interview procedures,* or observation of public behavior,* unless
 - a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects
 - b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if
 - a. the human subjects are elected or appointed public officials or candidates for public office
 - b. federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects
5. Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine
 - a. public benefit or service programs
 - b. procedures for obtaining benefits or services under those programs
 - c. possible changes in or alternatives to those programs or procedures
 - d. possible changes in methods or levels of payment for benefits or services under those programs
6. Taste and food quality evaluation and consumer acceptance studies
 - a. if wholesome foods without additives are consumed
 - b. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture

* Not applicable to surveys or interviews involving children or to "participant-observation" studies of children.

F. Research Exemptions in Social and Behavioral Research

The Common Rule at §____.101(b) defines six categories of human research that are exempt from its human subjects protection requirements (see Chapter 10 and Table 17.1, above). Many of these categories are likely to apply to certain social and behavioral sciences.

The exemptions most commonly relevant to social and behavioral research include certain research in the following categories:

- research in established or commonly accepted educational settings involving normal educational practices⁸
- research using educational tests; survey or interview procedures with adults; or the observation of adults' public behavior
- research using existing data, documents, or records

⁷ See www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html.

⁸ It is important to note that the U.S. Department of Education also complies with the Family Education Rights and Privacy Act of 1974, which is designed to protect student records from disclosure without consent from parents or students over 18 years of age. In addition, the Protection of Pupil Rights Amendment gives parents the right to consent for their children to participate in sensitive research. Individuals conducting research supported by the Department of Education must be aware of these requirements.

Exemption category 5, research and demonstration projects, is frequently a source of confusion for research managers trying to determine if protocols are exempt. Examples of exempt research include some studies of assisted living facilities by the Department of Veterans Affairs to determine the level of benefits and services or evaluations of Social Security numbers by the U.S. Census Bureau to assist in federal resource allocation decisions.

The IRB or a knowledgeable official designated by the institution, not the individual investigator, should determine whether research is exempt from the human subjects protection requirements. Investigators who believe their research satisfies the criteria for exemption must provide the appropriate written verification to the IRB (or designated official) and await an official response before involving subjects in the research.

It is important to emphasize that the official(s) designated by the institution to verify exemptions must be trained in the nuances of the human subjects regulations. Although it was once common for institutions to designate a number of such officials in a decentralized verification system, this approach has been abandoned by most institutions as ineffective, inconsistent, and prone to error. Most institutions now use a centralized mechanism in which a single individual or office verifies exemptions.

Points to Consider in Determining Whether Research in Educational Settings Is Exempt from the Common Rule

Social and behavioral research frequently examines educational practices. Research that is conducted in *established or commonly accepted educational settings* that involves *normal educational practices* is exempt from the Common Rule at §____.101(b)(1).

This is a broad exemption, in part because the terms *commonly accepted* and *normal* are somewhat subjective. Moreover, the examples given for “normal educational practices” (i.e., research on “regular and special education instructional strategies” and “instructional techniques, curricula, or classroom management methods”) are themselves rather broad.

Most IRBs consider *established or commonly accepted educational settings* to include but not necessarily be limited to:

- public or private preschools and kindergartens; elementary schools; middle schools, intermediate schools, and junior high schools; and colleges and universities

- technical schools
- continuing education and certificate programs
- distance learning programs
- hospitals, clinics, and counseling centers where education sessions are regularly conducted

Simply because a research project is conducted in an established education setting does not mean that the research is exempt from the requirements of the Common Rule. The research must involve the study of normal educational practices. Most IRBs consider *normal educational practices* to include but not necessarily be limited to:

**normal
educational
practices**

- instructional strategies and techniques such as lectures, discussions, individual and group projects, homework, nonstressful role playing, self-paced learning, peer instruction, and games
- content that is part of the established curriculum or that has been approved by the school board or education superintendent (that is, beyond the level of school principal or teacher) for investigation
- classroom management techniques such as nonpunitive behavior modification, peer mediation, anger or stress management programs, games and competitions, and individual and group motivation programs

In reviewing research in educational settings, it is important for IRBs (or the exemption official) to remember that the exemption does not apply if the setting is not commonly recognized as an educational one or if other-than-normal educational practices are employed.

Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected. If the research is not exempt under the conditions described above, the IRB may utilize expedited procedures (see Chapter 10) for the review and approval of educational research.

Exempt Research Using Educational Tests, Survey Procedures, Interview Procedures, or the Observation of Public Behavior

Social and behavioral research often utilizes educational tests (cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or the observation of public behavior. When research consists solely of such techniques, it may be exempt from human subjects protection requirements under §____.101(b)(2). However, there are important conditions and exceptions that make this exemption somewhat confusing:

Adult Subjects. When the subjects are adults, an exemption applies unless (1) information

is recorded in an identifiable manner (either directly or indirectly using codes or links to identifying information) and (2) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. The research is exempt unless both conditions apply.

Subjects Who Are Children. This exemption applies to research involving children, except

- research involving educational tests, survey procedures, or interview procedures with children is not exempt; and
- research involving observation of the public behavior of children is not exempt if the investigator participates in the actions being observed.

Public Officials. If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt under the Common Rule at §____.101(b)(3) when the subjects are elected or appointed public officials or candidates for public office.

Absolute Confidentiality. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is also exempt under the Common Rule at §____.101(b)(3) where federal statutes require confidentiality without exception.

If not exempt under the conditions described above, the IRB may often utilize expedited procedures for the review and approval of social and behavioral research involving the use of educational tests, survey procedures, interview procedures, or the observation of public behavior (see Table 17.2 for a list of expedited categories relative to social and behavioral science research; see also Chapter 10 for a more detailed discussion of expedited review).

Exempt Research on Existing Data, Documents, and Records

Social and behavioral research often relies on the analysis of existing data, documents, or records. Such research may be exempt if the data already exist at the time the research is proposed—that is, if the study is conducted retrospectively.

Retrospective studies are research studies that involve the review of data, documents, records (e.g., school records, employment records, medical records), or specimens *collected in the past and existing at the time the research is proposed*. These studies are exempt under §____.101(b)(4):

- if these sources are publicly available; or
- if the information is recorded by the investigator in such a manner that subjects cannot be identified either directly or through identifiers linked to the subjects.

This exemption can be confusing because OHRP has never formally defined *publicly available*. Most IRBs interpret publicly available to mean available to virtually anyone or available commercially.

publicly available

The exemption also can be confusing for investigators who confuse the concept of *anonymous data* with the concept of *coded data*. Coded data are not anonymous because there is a link (i.e., the code) through which subjects can be identified. However, codes included in public use datasets (see Chapter 13) are not considered identifiers unless the researcher using the data has the means to link the codes to the identifying information.

anonymous data

coded data

The exemption for existing materials permits investigators to obtain and view identifiable private information, but, in order for the research to be exempt, the investigator may not record or possess any codes, identifiers, or other linkers through which subjects can be identified.

Studies proposing to use materials that will “exist” in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do not qualify for exemption under exemption category 5, because the materials in these studies are not in existence at the time the study is proposed and initiated. Under some circumstances, the IRB may use expedited procedures (under expedited category 5 in Chapter 10) to review such research.

G. Expedited IRB Review of Social and Behavioral Research

Social and behavioral research that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998, *Federal Register*, “Notice on Expedited Review,” may be reviewed by the IRB utilizing expedited procedures (see Chapter 10) (OPRR 1998).

Table 17.2

Partial List of Research Categories That Qualify for Expedited Review

- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis) (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46). This listing refers only to research that is not exempt.)
- Collection of data from voice, video, digital, or image recordings made for research purposes
- Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects at 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Two important considerations must be noted with regard to expedited review. First, in order to be eligible for expedited review, the research must be both no more than minimal risk and must be included in the list of eligible categories of research. Not all minimal risk research is eligible for expedited review, and not all research included in the list is eligible. Second, expedited review is not “review light.” All of the regulatory requirements must be met for both expedited and full review. The only difference between expedited review and review by the full IRB is who conducts the review.

Three of the nine categories of research that may be eligible for expedited review are particularly relevant to social and behavioral research, including such research involving children but not research involving prisoners. These are discussed below and displayed in Table 17.2.

Expedited Review of Research Involving Collected Materials. Social and behavioral research sometimes utilizes identifiable materials (data, documents, records, or specimens) that have already been collected before the development and initiation of the research. Such research involving already-collected materials is said to be conducted using retrospectively collected data and may qualify for expedited review under expedited category 5 in table 17.2.

Social and behavioral research also may use materials that will be collected in the future for purposes unrelated to the research. Research involving materials to be collected in the future is termed *prospective*. Prospective studies are designed to observe outcomes or events (e.g., behavioral outcomes, physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research. Research involving materials (data, documents, records, or specimens) that will be collected in the future solely for nonresearch purposes also may qualify for expedited review under expedited category 5 in table 17.2.

prospective studies

The specific wording of expedited category 5 may be somewhat confusing. It is important for IRBs to note that the intent of the drafters of this category was to define two categories of minimal risk research, as follows, each of which is appropriate for expedited review:

1. nonexempt research involving materials that have already been collected (for any previous research or nonresearch purpose) at the time the research is proposed
2. nonexempt research involving materials that will be collected in the future for a nonresearch purpose

Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings for Research Purposes. Social and behavioral scientists frequently make audio-and/or videorecordings of subjects in the course of their research. The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes when these activities pose no more than minimal risk to subjects (expedited category 7 in Table 17.2).

Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies. Expedited category 7 was created specifically for social and behavioral research that poses no more than minimal risk of harm to subjects.

This category covers a wide range of activities, including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior.

H. Internet Research

There are two types of Internet research: research conducted on the Internet using the Internet as a tool and research studying Internet behavior. Internet research presents new concerns to the traditional IRB issues of risk-benefit, consent, participation by minors, privacy and confidentiality.

Research conducted on the Internet presents two possible sources of harm. One source is the harm that can befall subjects through participation in the research (e.g., adverse reactions to questions). The problem here is that the researcher has no direct interaction with subjects and cannot deal with individual reactions. The most likely source of harm, though, is through a breach of confidentiality. Breaches of confidentiality can occur inadvertently (e.g., an investigator who accidentally sends out an identifiable database to an

inadvertent and deliberate breach of confidentiality

entire Listserv) or through deliberate attempts to access information (hacking). Technology can provide reasonable security but cannot guarantee security.

Consent can be obtained in research conducted on the Internet by providing the required information to subjects and having a way, such as a check box, for them to indicate that they agree to participate. However, there is currently no way to comply with the regulatory requirements for the documentation of consent without having subjects sign a consent form. Current technology does not allow for acceptable digital signatures. In these cases, the IRB must waive the requirement for documentation of consent.

Another issue that must be considered in research on the Internet is the involvement of minors. It must be assumed that, unless elaborate screening procedures are used,

minors will participate in the research. There is no way of guaranteeing that the person who is completing a survey is, or is not, a minor. Therefore, the research that targets minors must be appropriate for that age group and meet the criteria for a waiver of parental permission.

When Internet behavior is the subject of the research, the primary concerns are privacy and confidentiality. Many consider much of the Internet as public space, making the study of Internet behavior observation of public behavior. The regulations define private behavior as "...information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place..." (§____.102(f)). Therefore, whether Internet behavior is public behavior depends on whether the subjects have a reasonable expectation of privacy. The question is not clear, and the IRB must address it before making a determination.

Online participants usually use pseudonyms (e.g., screen names, handles). Although not publicly linked to actual names, identities can often be "readily ascertained" (e.g., by using a search engine). Also, people's online identity may be as important to them as their actual identity. Therefore, the pseudonyms must also be considered confidential.

For Internet research, investigators are going to have to provide to the IRB technical information on how they will deal with these issues. IRBs need to have sufficient expertise on the technical aspects of the Internet in order to ask the right questions and evaluate the information provided. IRBs that review Internet research without sufficient expertise are not in compliance with the regulations.

Key Concepts: Social and Behavioral Research

- Social and behavioral research is typically designed to investigate social interaction or influence, cognitive or affective processes, or behavior.
- Common social and behavioral research techniques include surveys, individual and group interviews, individual and group observations, record and database analyses, experimental interventions, and manipulations of subjects' environment.
- Potential psychological harms include psychological discomfort, stress, anxiety, pain, trauma, guilt, or instability, all of which can range from mild to severe.
- Potential social harms include disruption of family and social relationships; stigmatization; damage to reputation, employability, insurability, or financial standing; and civil or criminal sanctions.
- Privacy addresses whether the investigator has legitimate access to information for research purposes. Confidentiality addresses whether there are sufficient protections against unauthorized disclosure of information once it has been obtained.
- To protect the confidentiality of information, IRBs should require specific descriptions of confidentiality protections as well as instances in which confidentiality will not be maintained in the project plan and informed consent process.
- A certificate of confidentiality protects the researcher against involuntary disclosure of subject information resulting from a compulsory legal process.
- The IRB (or an official designated by the institution [not the investigator]) determines if research is exempt from human subjects protection requirements. It is extremely important for the designated official to be well trained regarding human protection requirements, and most institutions now use a centralized mechanism for verifying exemptions.
- Research that is conducted in *established or commonly accepted educational settings* that involves *normal educational practices* is exempt.
- Research with adult subjects that utilizes educational tests (cognitive, diagnostic, aptitude, and achievement tests), survey procedures, interview procedures, or the observation of public behavior is usually exempt, unless the information collected is both identifiable and sensitive.
- Research involving surveys or interviews with children is not exempt nor is research involving observation of the public behavior of children if the investigator participates in the actions being observed.
- Research involving the collection or study of existing data, documents, or records (or pathological or diagnostic specimens) is exempt, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects. This exemption permits investigators to view identified information but forbids the investigator from recording or possessing any codes, identifiers, or other linkers through which subjects can be identified.
- Nonexempt, minimal risk research involving materials that already have been collected (for any previous research or nonresearch purpose) at the time when the research is proposed may be reviewed using expedited procedures.
- Nonexempt, minimal risk research involving materials that will be collected in the future for a nonresearch purpose may be reviewed using expedited procedures.
- Minimal risk research that involves the collection of data from voice, video, digital, or image recordings made for research purposes may be reviewed using expedited procedures.
- Minimal risk research involving individual or group characteristics or behavior; or employing survey, interview, oral history, focus group, program evaluation, or human factors evaluation; or quality assurance methodologies may be reviewed using expedited procedures.
- To approve research involving deception, the IRB must find and document in a protocol-specific fashion that all four of the following criteria have been satisfied:
 1. The research presents no more than minimal risk to subjects.
 2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
 3. The research could not practicably be carried out without the waiver or alteration.
 4. Where appropriate, the subjects will be provided with additional pertinent information after participation.

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Chapter 18

Research on Specimens, Data, Documents, or Records

- A. Introduction
- B. Conceptual Overview
- C. Existing Regulations/Guidance Related to the Use of Specimens and Associated Data for Research
- D. Institutional Review Board Considerations
- E. Issues for Investigators: Practical Considerations for Researchers Establishing and Operating Human Specimen and/or Data Repositories

Key Concepts

References



A. Introduction

The development of powerful molecular technologies has increased the use of human specimens and their associated data in research. In addition, computer technology has facilitated the access to and sharing of data, documents, and records about individuals for research purposes. The power of these technologies has increased concern about their implications for the subjects from whom the specimens and/or data are obtained. Although much specimen or data research does not involve direct interaction with subjects or physical risks, other risks to subjects, such as loss of privacy and confidentiality and psychosocial risks, raise a variety of legal and ethical issues about the use of specimens and the associated data. These issues have been the subject of considerable discussion and were addressed in the report of the National Bioethics Advisory Commission (NBAC), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), in the Department of Health and Human Services (DHHS) response to the NBAC report and in the report of the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group (2007).¹ Although these reports do not represent official policy guidance and have no regulatory status, they do present a comprehensive discussion of the various issues related to the use of human specimens in research.

This chapter discusses a number of aspects related to research using human specimens and/or data, including the benefits and risks to subjects, legal and ethical issues, and existing guidance and regulations. It also will provide practical considerations for Institutional Review Boards (IRBs), individuals who manage specimen databanks and/or repositories, and researchers who use specimens and data in their work. Research on embryonic stem cells, fetal tissue, and the use of human tissue/organs for transplantation purposes requires special consideration (see Chapter 26 of this resource manual for a discussion about research involving embryonic or fetal material). It should be noted that the legal, ethical, and policy issues related to the use of specimens and data is a rapidly evolving area. Thus, IRBs, researchers, and repository managers should regularly check the Web sites for the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and other sources for the latest information on relevant regulations, guidance, and policy issuances related to this topic. Of note, the Office for Human Research Protections (OHRP) issued *Guidance on Research Involving Coded Private Information or Biological Specimens* in 2008.

¹ See <http://aspe.hhs.gov/sp/hbm/report.htm>.

B. Conceptual Overview

Types of Specimen and Data Collections

Many types of human biological specimens can be used for research, including bodily fluids, such as blood, saliva, cheek swabs, and urine, or tissue, such as normal skin or tumor tissue. Specimens are sometimes subjected to further processing to isolate molecular components such as DNA and RNA or to establish cell lines. Information about the individual from whom the specimen and/or data is obtained also may be collected, including demographic and/or lifestyle information and family and/or medical history.

Specimens and data can be collected prospectively or from existing pathology archives. They can be collected specifically for research purposes or during the course of residual material remaining after the removal of a tumor or other diseased tissue. The most common sources of human biological materials are diagnostic or therapeutic interventions during which diseased tissue is removed or tissue or other material is obtained to determine the nature and extent of a disease. Even after the diagnosis or treatment is complete, a portion of the specimen is routinely retained for future use. Specimens also are obtained during autopsies. In addition, volunteers donate organs, blood, or other tissue for transplantation or research, and some donate their bodies after death for transplantation of organs or anatomical studies.

The specimens and/or data can be organized into different types of collections—for example, individual, private collections residing in a single investigator’s laboratory or large, well-curated repositories or collections of specimens and/or data that are used by multiple researchers, each with separate research projects. Some repositories or databases collect specimens and/or data specifically for distribution to researchers. Other repositories or databases serve as central storage and distribution facilities for specimens and/or data collected specifically for individual research projects, multiple research projects, or clinical trials. Repositories might have a single collection site or multiple collection sites.

Specimen collections can have varying amounts of associated data, with or without subject identifiers. Collections used for basic and developmental studies might have only associated demographic and histopathological information, while collections from clinical studies might be annotated with large amounts of clinical and outcome data. Some specimen and/or data collections might be completely anonymous, providing no way to trace the identity of donor subjects. Others may be coded, in which a link is maintained

human biological materials

coded data or specimens

to subject identity, but no identifying information is available to the researcher receiving the specimens. Specimens and/or data may also be “identified” in that they are associated with direct personal identifiers (such as names or patient numbers) such that additional information can be obtained on the donor subjects in the future.

With the development of advanced DNA sequencing technologies, in theory, a biospecimen stripped of all identifiers could be identified if there was a referent sample available for comparison. However, currently such identification is beyond the capacity of most investigators.

Research use of medical data is not always tied to specimens. Research sometimes relies on the use of large existing datasets, such as immunization records, Medicaid or Medicare usage records, or epidemiologic research documentation. Such research might be used to track disease trends, make public health decisions, or plan future research. The use of these kinds of datasets does not usually involve direct interaction between investigators and the individuals who are the source of the data.

Benefits of Specimen and Data Research

The primary benefits of specimen research are societal. The availability of human biological specimens and the associated data are critical to making progress in scientific research, continuing to make medical advances, and translating basic discoveries into patient care. Historically, the science of pathology has led the way in the investigation of the mechanisms of disease causation by progressing from a focus on whole organs and tissues to cells and then from the subcellular to the supramolecular and molecular manifestations of disease expression. Research in cancer, infectious diseases, and mental disorders is advanced by access to such materials. In addition, large, longitudinal studies that aim to investigate the causes of diseases in certain populations over time depend on a continuous source of biological materials for study.

Historical reports have illustrated some of the advances made possible by specimen research, including progress in the area of cancer research, improved diagnostics, and insight into the effects of environmental toxins on health. Although the direct physical benefits of specimen research to individual donor subjects are likely to be limited, they may include psychosocial benefits, such as a sense of empowerment and a feeling of having made a valuable contribution to society by donating specimens for science and medical research. This may be particularly true in the case of subjects with serious illnesses.

Risks to Subjects

OHRP guidance defines “coded” as meaning:

- (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and
- (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Potential risks to subjects whose specimens and the associated data are used in research may include physical risks, particularly if the specimens are taken specifically for research purposes. Physical risks can include those involved with medical procedures, such as blood draws or extra biopsies taken for research purposes. Often, however, residual specimens taken during the course of routine medical care (e.g., diagnostic specimens) are used for research, which means that additional physical risk beyond that involved in the diagnostic procedure is not incurred.

Nevertheless, it is critical to ensure that patient diagnosis and care will not be compromised as a result of the use of these specimens for research.

Advances in genetic and other molecular technologies have heightened concerns about the risks of specimen research, particularly in the areas of privacy and confidentiality. This is because research involving specimens has the potential to identify genetic or other molecular alterations that may have implications for an individual's current or future health, such as the presence of disease or other unsuspected risks. In addition, the improper use or disclosure of such information could result in psychosocial harms (such as anxiety) or the loss of employment or insurability. Information concerning hereditary characteristics also may have implications for family members. (See Chapter 24 for a more complete discussion of this subject.)

potential to identify genetic or other molecular alterations

such as the presence of disease or other unsuspected risks. In addition, the improper use or disclosure of such information could result in psychosocial harms

An additional risk to subjects involves the improper use of unvalidated research results obtained from specimen research for clinical decisionmaking. This includes the use of test results for patient treatment and care when tests have not been

Clinical Laboratory Improvement Amendments

shown to have clinical validity or utility. Also, tests should be performed in Clinical Laboratory Improvement Amendments

(CLIA)-certified laboratories, and in some cases, require FDA approval (as in test kits.) Consequently, care should be taken to protect subject privacy and confidentiality and to avoid the improper disclosure or use of individual research test results to ensure that they are not used for medical decisionmaking.

Research on human biological specimens and/or the associated data also may involve risks to groups of individuals. For example, research using specimens may determine that a particular group of individuals (for example, a specific ethnic group) has an increased risk of developing disease. Disclosure of such information could have implications for insurability and/or employment and the potential for stigmatization. Such risks need to be considered, and care must be taken to minimize them in research study design.

Despite these potential risks, NBAC, in its report *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), noted that a great deal of the specimen research that is conducted should be considered minimal risk research. It is difficult to document any instances in which individuals have been harmed as a result of confidentiality breaches in a research setting. Even so, risks to privacy and confidentiality must always be considered in research involving specimens and/or the associated data. (Further discussion of these issues is included in later sections of this chapter and in Chapters 13 and 24.)

In cases in which large datasets are used for research, the investigator is not likely to have any direct contact with the individual identified with the data, and the primary ethical concerns are threats to privacy and confidentiality from accidental or inappropriate disclosures of information. In such cases, security during the storage, access, transmission, and management of data become important issues to consider in protecting privacy and confidentiality.

Respect for Persons

Another ethical consideration beyond the risks and benefits of the research is the respect for autonomy of the subject from whom the specimens or data are obtained. Respect for persons is part of the moral justification for requiring informed consent in research and is fundamental for maintaining the public trust. In particular, certain individuals may have religious or cultural beliefs related to their body parts or the use of their specimens. For example, some individuals or groups, such as Native Americans, may have strong beliefs about the integrity of the body, whether living or dead (NBAC 1999). Individuals and groups also may have an interest in the types of research for which their specimens and data will be used. Some individuals or groups might find certain types of research objectionable, such as contraceptive research or research on putative

biological markers of violence or other socially unacceptable behaviors. These issues need to be carefully considered by investigators when designing such research projects and by IRBs when reviewing research protocols involving the collection and use of specimens for such research.

Exactly how much control an individual should have over the use of his/her specimens and data is an area about which there is little guidance or clarity and is the subject of considerable debate. However, respect for persons must always be considered in the ethical review of all research, including research on specimens and/or data.

C. Existing Regulations/ Guidance Related to the Use of Specimens and Associated Data for Research

Research using human specimens and the associated data may be subject to federal regulations as well as to state and local laws. The Common Rule governs research using individually identifiable specimens and associated data that is funded by any one of the 17 agencies that have adopted the Common Rule. DHHS has additional protections for special populations that also may apply (45 CFR 46, Subparts B, C, and D).² As discussed in further detail below, research using specimens and/or data that will be used to obtain FDA approval or research that is subject to FDA oversight is governed by similar regulations.

Determining When Research Using Human Specimens, Data, and Documents Involves Human Subjects

The Common Rule defines a human subject as “a living individual about whom an investigator obtains either 1) data through intervention or interaction with the individual, or 2) identifiable private information” (§____.102(f)). Federally conducted or supported research that does not involve interactions or interventions with living individuals or obtaining identifiable private information is not considered human subjects research. Therefore, under the Common Rule, research using biological materials from which the identity of the subjects cannot readily be ascertained by the investigator is not considered human subjects research. Specimens or associated data that are obtained from deceased individuals (e.g., autopsy materials) or are truly anonymous are not covered by the Common Rule, but other federal regulations and state and local laws may apply.

In contrast, FDA regulations define a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient” (21 CFR 50.3(g)); or “a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.” (21 CFR 812.3(p)).³

Federally conducted or supported research that uses human specimens and/or data in cases in which the subjects may be identified by the investigators is considered human subjects research that is governed by the Common Rule. IRB review and approval is required for such research. In addition, research that uses human specimens and/or data that contain links (such as a code) to identifying information are also generally considered to involve human subjects.

However, in certain circumstances, research using specimens and data in which links to identifying information are maintained is not considered human subjects research. OHRP does not consider the act of solely providing coded private information or specimens (e.g., by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, OHRP would consider such additional activities to constitute involvement in the conduct of the research.

OHRP recommends that institutions have policies that identify the individual or entity authorized to determine whether research involving coded specimens and/or data constitutes human subjects research and that investigators not be given the authority to make such determinations independently. In these situations, an institution or an IRB could determine that IRB review of the research using the specimens and/or data is not needed.⁴

Exempt Research Versus Nonexempt Research

Research with specimens and/or data from living individuals does not require IRB approval under the Common Rule when it is determined that the research is in one of the exempt categories listed in the Common Rule. The exemption that is most pertinent for research using human specimens and/or data is known as exemption #4. As stated in the Common Rule at §____.101(b):

² See <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>.

³ The reader is encouraged to regularly consult the FDA Web site at www.fda.gov for any additional guidance regarding these or other regulations or requirements.

⁴ OHRP Guidance on Research Involving Coded Private Information or Biological Specimens dated October, 2008, available at <http://www.hhs.gov/ohrp/policy/cdebiol.html>.

Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The phrase “publicly available” originally was intended to apply to public sources of data. Many organizations make human cells and tissues broadly accessible at reasonable cost to the research community. However, the specimens are provided only to investigators with bona fide research projects and are not usually available to the public at large. These types of collections are not generally considered to be publicly available.

It is important to note that the specimens and/or data must be “existing” in order for exemption 4 to apply. This means that the specimens should be existing (“on the shelf” or in the freezer) at the time the protocol is submitted to the IRB to determine whether the research is indeed exempt. Not all studies on existing specimens and/or data are exempt. For example, the exemption does not apply if the researcher will record subject identities or other identifying information that could be used to identify the subject, even if the specimens would otherwise be discarded. Identifiers such as names, Social Security numbers, medical record numbers, or pathology accession numbers permit specimens to be linked to individuals and perhaps also to associated medical information. It should be noted that DHHS-supported research involving prisoners is not eligible for any exemptions. Thus, research using identifiable specimens and/or data from living subjects who are prisoners is not eligible for exemption 4, even if the specimens and/or data are recorded in such a way that the subjects from whom the specimens are obtained cannot be identified.

Sometimes the distinction between when research is exempt under exemption 4 and when it does not involve human subjects at all is unclear. Research involving only the use of anonymous specimens and/or data, in which no identifying information is retained that would allow anyone to trace the identity of the subjects from whom the specimens and data were obtained, is not considered human subjects research. If, on the other hand, the researcher or other individuals engaged in the research initially have access to identifying informa-

tion about the subjects but will record the information in such a way that the subjects cannot be identified, the research, while human subjects research, qualifies for exemption 4. In making these determinations, it is helpful first to ask whether the research involves human subjects, and if it does, then ask whether or not it qualifies for an exemption.

Determining when research using human specimens and/or data is human subjects research and thus subject to federal regulations can be complex. Therefore, someone other than the investigator should make these determinations. In order to ensure that the research is appropriate for an exemption, OHRP advises (and many institutions require) an IRB or an appropriately trained institutional official to make the determination.⁵ OHRP has published decision charts to help IRBs and researchers make these decisions.⁶

Although research that is not exempt may require informed consent from the person from whom the specimens and/or data were obtained, an IRB may waive the requirement for informed consent if the risk to the subjects is minimal and if the criteria for waiver of consent specified at §____.116(d) have been met. (See the discussion of consent below.)

Records Research Under the Common Rule

The review of medical records for research purposes is exempt under the Common Rule if the information is recorded by the investigator in such a way that it does not identify the patient. However, institutional procedures and requirements related to records research vary; some institutions may require IRB review and approval for such research. Much records research may qualify for expedited IRB review at §____.110 and pursuant to the list of research eligible for expedited review provided on the OHRP Web site.⁷ This issue also is addressed in Chapter 11 on IRB review.

FDA Regulations

In addition to the Common Rule, FDA regulations also may apply to research using human specimens and the associated data. FDA regulations generally apply to biomedical research for completing a marketing application to FDA or for research used to develop FDA-regulated products. For example, the FDA regulations may apply to research that uses human specimens and associated data to develop and/or validate diagnostic assays for which FDA approval will be requested.

FDA regulations differ from the Common Rule with regard to the criteria for waiver of informed consent or IRB review (Moxey-Mims et al. 2001). Section 520(g) of the Federal

⁵ See <http://www.hhs.gov/ohrp/policy/hssc95-02.html>.

⁶ See <http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html>.

⁷ See <http://www.hhs.gov/ohrp/policy/expedited98.html>.

Food, Drug, and Cosmetic Act, which provides regulations for investigations of medical devices (which may include diagnostic tests), requires that IRB review (520(g)(3)(A)) and informed consent (520(g)(3)(D)) be obtained for all clinical investigations of medical devices, except in certain emergency circumstances. Regulations for the implementation of these sections of the act are provided in 21 CFR Parts 50, 56, and 812.⁸ The Common Rule provides for waiving or altering elements of informed consent for minimal risk research if the conditions of 46.116(c)&(d) have been met, permitting the waiver of the informed consent requirement. On April 25, 2006, FDA issued new guidance to inform sponsors, IRBs, clinical investigators, and agency staff that it intends to exercise enforcement discretion, under certain circumstances, with respect to its current regulations governing the requirement for informed consent when human specimens are used for FDA-regulated in vitro diagnostic (IVD) device investigations. In this guidance, FDA states that it “does not intend to object to the use, without informed consent, of leftover human specimens—remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded—in investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable.” Specimens obtained from “specimen repositories and specimens that are leftover from specimens previously collected for other unrelated research” are included in this policy as long as the specimens are not individually identifiable.⁹

Federal Privacy Regulations

Data maintained in a covered entity that contains identifying information may be subject to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. DHHS issued the Privacy Rule¹⁰ on August 14, 2002 (see Chapter 13 for a more extensive discussion). This federal regulation governs the protection of individually identifiable health information and was enacted to increase the privacy protection of health information with individual identifiers and to regulate known and unanticipated risks to privacy that may accompany the use and disclosure of such identified personal health information. It covers individually identifiable health information that is held or maintained by “covered entities” (health plans, health care clearinghouses, or health care providers who transmit health information for certain transactions as defined by DHHS) or by business associates acting for a covered entity. The Privacy Rule does not apply to specimens per se, but it may apply to the identifying information associated with specimens.

In contrast to the Privacy Rule, the Common Rule (_____.102(f)) does not consider coded private information to be identifiable if the investigator cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimen belongs. Therefore it is possible that some coded information would be individually identifiable under the Privacy Rule but not under the Common Rule.

The Privacy Rule generally requires authorization from individuals to use their protected health information in research, unless an exception applies. This authorization is distinct from informed consent, which is a separate process. The DHHS Office for Civil Rights has published a series of educational documents that can be obtained from its Web site.¹⁰ (See also Chapter 13.)

State and Local Laws

In addition to federal regulations, state and local laws that may apply to the use of specimens and/or data for research should be considered. These include human subjects protection laws, laws regulating genetic testing or genetic information, laws that prohibit genetic discrimination (such as insurance and employment laws), general privacy or health privacy laws, public health regulations, and medicolegal requirements, such as record and sample retention. IRBs may wish to consult with the legal offices of their institutions to determine how these regulations apply to research on records, documents, and specimens.

OHRP's Model and Tissue Repository Guidance

Several models exist for protecting subjects whose specimens and associated data are collected by repositories and used for research. OHRP has included a model and additional guidance for repositories on its Web site.¹¹ In this model, illustrated in Figure 1, above, the repository's IRB reviews and approves the repository's operating procedures and policies for protecting donor subjects, including the informed consent process. Each collecting site has an approved assurance from OHRP. IRB review and informed consent is required at the collection site, unless the IRB has approved a waiver of informed consent. In this model, investigators who are not receiving identifiable data need not obtain IRB review and approval because there is agreement from the recipient investigator that he/she will abide by the human subjects regulations and will not to try to identify donor subjects.

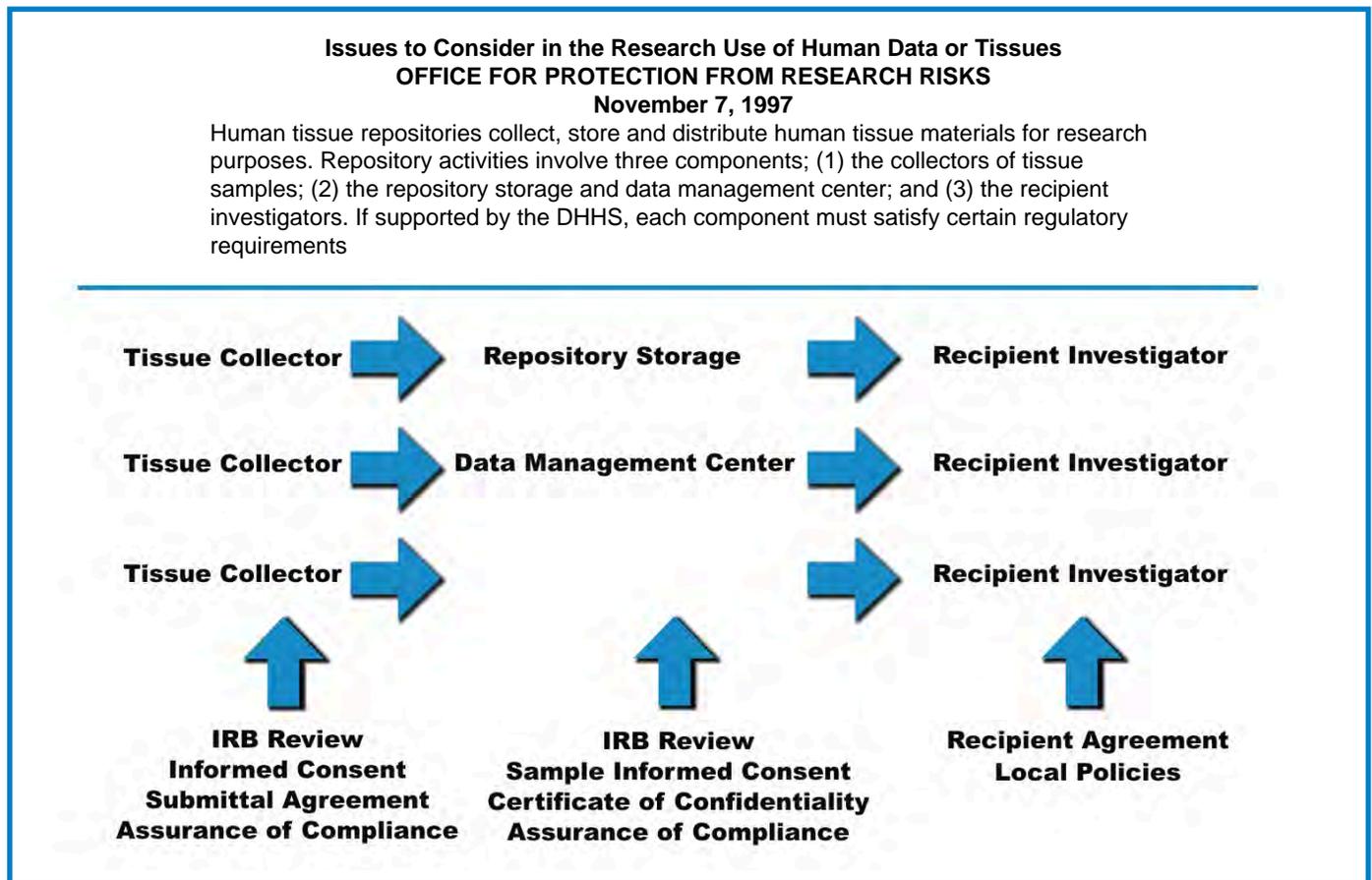
⁸ See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm>.

⁹ See <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf> for the complete guidelines.

¹⁰ See www.hhs.gov/ocr/.

¹¹ See <http://www.hhs.gov/ohrp/policy/reposit.html>.

Figure 1. OHRP Guidance for Repositories



Legend: Operation of the repository and its data management center should be subject to oversight by an IRB. The IRB should review and approve a protocol specifying the conditions under which data and specimens may be accepted and shared and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB should also review and approve a sample collection protocol and may choose to develop a sample informed consent document for distribution to tissue collectors and their local IRBs. A certificate of confidentiality may be appropriate in certain circumstances to protect the confidentiality of repository specimens and data.

Source: <http://www.hhs.gov/ohrp/policy/reposit.html>.

Honest Broker Model for the Protection of Specimen Donor Subjects

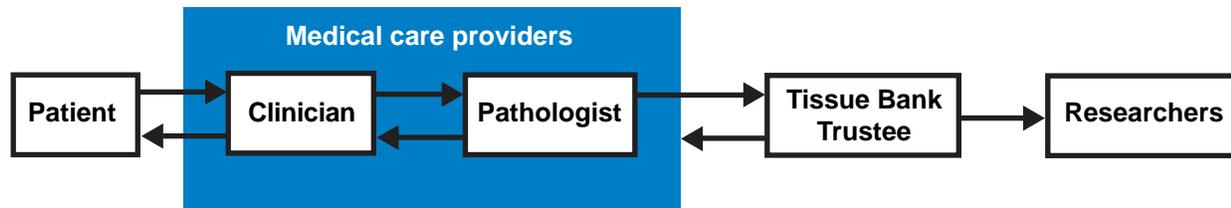
A paper by Merz et al. (1997) proposes an “honest broker” model, as illustrated in Figure 2. In this model, the repository functions as a “tissue trustee” with the role of protecting donor subjects. The trustee serves as an intermediary between the tissue sources and the researchers to control access to subject data associated with the tissue and protect the privacy of subjects while facilitating research. The honest broker model allows a one-way flow of information from the tissue bank trustee to the researcher. The tissue trustee deidentifies the specimens and data provided to researchers by removing directly identifying subject information. However, the specimens and data provided to the researcher could include a linking code that would allow the specimens and data to be reidentified but only by the tissue trustee. Such a model protects the identities of subjects from the researcher, while permitting

additional follow-up data to be obtained when needed. This approach has been further explored by Dhir et al.

D. IRB Considerations

A wide variety of protocols involving specimens and data may be submitted to the IRB for review, such as those for the operation of a specimen and/or data repository, which include procedures for the collection and storage of such specimens and data and distribution to other researchers. Other protocols may involve specific research projects that also involve the establishment of a specimen or databank for the same or other research projects as well as protocols from researchers who are not collecting specimens and/or data themselves but are using specimens and data obtained from other investigators or from existing banks or tissue procurement systems.

Figure 2. Honest Broker Model for Protecting the Privacy and Confidentiality of Donor Subjects



Legend: Interposing a tissue bank trustee between patients and their caregivers and biomedical researchers enables strict control of information flows (arrows) associated with research using banked tissues.
Source: Merz et al. 1997.

Use of Expedited Review Procedures

Research on data, documents, and specimens may be reviewed by the IRB through an expedited review procedure (see Chapter 10) if it presents no more than minimal risk to human subjects and involves only procedures that are on the list of activities included in the OHRP guidance on expedited review.¹² This list includes the following specimen and data collection activities:

- collection of blood samples by a variety of procedures if certain conditions are met
- prospective collection of biological specimens for research purposes by noninvasive means
- collection of data through noninvasive procedures routinely employed in clinical practice and research involving data, documents, records, or specimens that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)
- collection of data from voice, video, digital, or image recordings made for research purposes

When determining whether an expedited review is appropriate, the level of risk involved in the specific research that will use the data, documents, and/or specimens needs to be carefully considered. Although much research involving these activities may be categorized as minimal risk, some research may be of greater than minimal risk and thus may not be eligible for expedited review. For example, research involving the collection of blood for studies that include the analysis of an individual's HIV status or for studies of some heritable genetic disorders might be considered more than minimal risk, depending upon the type of information collected and maintained, the nature of the studies, and systems and policies to protect subject privacy and confidentiality. (See the expanded discussion of risk below).

Informed Consent

The need to obtain informed consent for the use of specimens and data depends on a number of issues, including whether the definition of a human subject has been met and whether the specimens and data can be readily linked to living individuals. If the samples and/or data are collected for research purposes or are associated with information that can identify the donor, then informed consent must be obtained from the donor unless it is appropriately waived by the IRB. If the research involves no interaction with the individual from whom the specimens and data are derived and the specimens and/or data cannot be linked to patient identities, then it does not meet the definition of human subjects research and informed consent is not required.

Waiver of Informed Consent: Assessment of Risk

Research using specimens where consent may be difficult to obtain may be able to be managed by looking into the availability of a waiver of informed consent. The Common Rule at §____.116(d) allows waiver of informed consent if the following conditions are met:

- research poses minimal risk to subjects
- research would not adversely affect subject's rights and welfare
- research could not practicably be carried out otherwise
- whenever appropriate, the subjects would be provided with additional pertinent information about participation

What constitutes minimal risk research and when it is appropriate to return individual research results to subjects are areas of considerable debate, as discussed below. Although the NBAC recommendations do not carry regulatory status or constitute official guidance, the commission recommended that, in most cases, the criterion of providing the subjects with additional pertinent information after participation usually does not apply to research using human biological materials (NBAC

¹² See <http://www.hhs.gov/ohrp/policy/exprev.html>.

1999). As noted previously, informed consent for research that is subject to the FDA regulations may be waived only under emergency circumstances.

An assessment of the level of risk to subjects is critical to determining whether informed consent for the use of specimens and the associated data can be waived. The Common Rule at §_____.102(i) defines “minimal risk” as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Risk is often difficult to assess for research involving specimens and the associated data. There can be physical risks to subjects if specimens are taken specifically for research purposes (blood taken by venipuncture or extra biopsies). However, the primary risk to subjects in the case of the use of residual specimens taken during the course of routine care is the loss of privacy and confidentiality.

Because most specimens contain DNA, the possibility that alterations in a person’s genes may be found accidentally or intentionally during research on these materials has caused some concern. Measurements of components other than DNA, such as those in blood, also may identify the presence of unsuspected disease or other risks to an individual. Common questions in this area relate to the use of information generated by the research and whether the research findings place the individual whose specimen is being studied at increased risk of harm.

It is usually easy to determine whether the risks associated with research that involves direct interaction with an individual conforms to the definition of minimal risk as stated above. The risks associated with research that does not involve any direct interaction with an individual are less obvious, making the assessment of the first waiver criterion—research posing minimal risk to subjects—more difficult. NBAC concluded that if the yardstick of risks commonly encountered in everyday living were applied to research on human specimens, most studies could be considered minimal risk. It did, however, identify a series of risks related to some studies of heritable traits, including stigmatization, discrimination in insurance and employment, and family conflicts (NBAC 1999). In addition, there is the risk of losing privacy as the result of research conducted on human specimens if care is not taken to prevent personal information from being disclosed inappropriately.

The two major sources of risk from research on human specimens and/or data are:

- the potential release or misuse of personal information associated with the specimen as it is collected, stored, and distributed to researchers

- the potential misuse of the research data produced from the study of the specimens and/or data—for example, the use of unvalidated research findings for clinical care.

Factors to consider in evaluating risks include physical risks (if any), the identifiability of the subject, the sensitivity of the subject data linked to specimens, the population under study, the subject matter of the research, and the likelihood of disclosure of research and/or subject information. An assessment of risk may be based on the following considerations.

Physical Risks. Research during which specimens are taken specifically for research purposes may involve physical risks. These may occur as a result of venipuncture or may be associated with extra biopsies that are taken specifically for research purposes. When residual specimens from medical procedures are being used for research purposes, care must be taken to ensure that the specimen is used first and foremost for patient care and that patient diagnosis and care are not compromised by use of the specimen for research.

Identifiability. Privacy risks associated with the use of specimens and/or data are generally proportional to how easily the specimens and the associated data may be identified with the subject. In general, the more identifiable the specimens and data and the greater the access to linkages to subject identities, the greater the privacy risk. Identifiability is determined by the specificity and nature of the data collected, the links to subject identity, and the degree to which the investigator has access to subject data, as well as other characteristics that alone or in combination may allow the subject to be identified. An evaluation of risk should consider both direct and indirect identifiers, such as name or date of birth, or identifying numbers, such as hospital identification number or Social Security number.

Other issues to consider are whether links are maintained to the identity of the subjects and whether characteristics of individuals or groups are used that would allow ready identification (such as specimens or data from patients with rare diseases or from readily identifiable populations). In general, completely unlinking (or anonymizing) samples reduces the risk to the individual who is the source of the sample—that is, if the process of anonymization is effective.

The degree of access that the researcher has to the subject data is another important consideration. The degree of access to subject identities would be affected by the proximity of the researcher to data systems containing patient identifiers, the relationship of the researcher to those who maintain identifiable subject data, the location of the research site relative to the location of the data, and the kinds of controls or firewalls that are in place to protect the data.

Sensitivity of the identifiable data. Certain types of data have a greater potential for harm than others if privacy and confidentiality are breached. For example, data on a person's gene for eye color is not likely to cause harm even if it were inadvertently released, but the release of an individual's HIV status could potentially cause considerable harm, including anxiety, stigmatization, and/or loss of insurability.

Nature of the research. The nature of the research also is an important consideration, as some kinds of research may be of inherently greater risk than others because of increased likelihood of stigmatization, psychological harm, or employment and/or insurance discrimination. In addition, research could more likely cause harm when unvalidated results are used to make clinical decisions. Some research on heritable genetic disease could impose greater risk because of its implications for family members, although genetic research does not necessarily present a greater risk than nongenetic research. In assessing risk, the IRB should consider the likelihood of harm, not whether or not the research is classified as genetic. As for all kinds of research, risk can vary greatly among studies and depends on factors such as the penetrance and seriousness of the condition.

Likelihood of disclosure of research and/or subject information. The likelihood of improper disclosure of the research and/or subject information is also important to consider. Having appropriate systems and policies in place to protect privacy and confidentiality can minimize the likelihood of disclosure of information. An IRB should examine a repository's policies for protecting privacy and confidentiality, such as the security of specimens and/or data and systems used to protect against research and subject information being provided to third parties (use of the honest broker model, encryption technologies, employee confidentiality agreements, Certificates of Confidentiality, and recipient agreements). IRBs also should consider a repository's policies for the return of individual research results to subjects or physicians.

In summary, while certain types of specimen research may impose greater risk than others, primary consideration should be given to the probability and magnitude of harm resulting from the research. NBAC concluded that much of the research using human biological materials may be considered minimal risk if the research adequately protects confidentiality and does not involve the inappropriate release of information to third parties and the study design includes an appropriate plan for whether and how to reveal findings to the subject and his/her physician, should the findings warrant disclosure (NBAC 1999). As in all research involving human subjects, the risks must be balanced against the benefits anticipated from the research results. In addition, the researcher must include in his/her proposal a clear description of the plans for minimizing risks.

Elements of Informed Consent

Informed consent is required when the IRB has determined that the research project involving human specimens and/or data from identifiable, living individuals involves more than minimal risk, or it does not meet the waiver criteria of applicable human subjects regulations. The nature of the informed consent process and form will vary widely depending on whether the specimens are being taken for a specific research project, whether the research also involves some experimental treatment, or whether residual specimens remaining from routine medical care are being collected for future unspecified research use.

It is important to make sure that the informed consent forms are clear and understandable and that the consent process provides the subject with the information needed to make an informed choice about whether to provide specimens and/or data for research. Most believe that consent for the collection, storage, and research use of tissue should be explicit and separate from routine surgical consent and should be provided either as a separate document or as a separate section of the same document.

Informed consent for the use of specimens and/or data should include the elements required by federal regulations (see Chapter 12) and state and local laws. A number of other elements also may be desirable. Informed consent for the use of specimens and/or data should include a clear description of the types of research that will be conducted with the specimens and/or data. The risks of the research should be described, including any psychosocial or privacy risks. When human hereditary genetic research is anticipated, informed consent should include information about the consequences of any DNA typing (e.g., possible paternity determinations). If the specimens and/or data will be held in a repository for distribution to other researchers, an overview of the purpose and use of the repository should be included, as well as the conditions under which the specimens and/or data will be released to recipient investigators. Procedures for protecting the privacy of subjects and maintaining the confidentiality of data also should be described.

Informed consent for the use of specimens and associated data should include the right of subjects to withdraw their consent at any time and should clearly define the logistics of such withdrawal. In many cases, it may not be possible to retrieve specimens and/or data once they have been released to recipient investigators. If so, this should be explicitly stated in the consent. For material that will be anonymized, donors should be informed that they will not be able to withdraw the specimens. Plans for returning research results, if any, also should be described.

Informed Consent for Prospectively Collected Specimens and/or Data. For identifiable specimens collected prospectively during the course of routine medical care, a consensus is emerging that consent beyond that contained in the general surgical consent is desirable. In the case of specimens and data collected prospectively for a specific research project, the informed consent should describe the research in sufficient detail for the subject to weigh the possible risks and benefits associated with participation in the research.

Informed Consent for Future Research Use. Often, when specimens are banked, the specific research that will be performed using the specimens and data is not known at the time of collection. For example, tissue remaining after routine medical care (biopsies, blood tests) may be stored for future research use.

The National Cancer Institute (NCI), together with the National Action Plan on Breast Cancer (NAPBC), has developed an approach for obtaining consent when the specific research use is not known at the time specimens are collected for routine care (Taube et al. 1998; National Cancer Institute Best Practices for Biospecimens Resources 2007). This approach involves the use of a model informed consent document and an accompanying patient information sheet that can be modified to meet institutional or study requirements.¹³ The consent form was developed by a group that included patient advocates, ethicists, lawyers, pathologists, clinicians, and laboratory researchers. The form has all the elements of consent required by the Common Rule and has been tested in 27 focus groups representing men and women as well as different socioeconomic levels, racial and ethnic groups, and professional and patient groups. The documents are written to be understandable for those with a low level of literacy.

The model informed consent and accompanying patient information sheet are designed to be used together. The subject information sheet, which should be given to the patient before administering the consent, helps to explain why and how tissues are used in research. The documents can be modified as appropriate for the anticipated research use of the specimens and as required by IRBs.

This consent uses a “tiered approach”—that is, it offers subjects the opportunity to allow their specimens and data to be banked and used for certain types of research (such as cancer and heart disease) as well as the opportunity to agree to be recontacted for permission to participate in future research studies. This approach has been found to be acceptable by a wide variety of groups, including patient and advocacy groups and NBAC. It has been successfully implemented by a number of the NCI Clinical Trials Cooperative Groups (Malone et al. 2002).

Some have argued that consent for the future use of specimens is not sufficient because patients are not provided with the specific details of each anticipated research study. However, recent studies suggest that many patients find consent for future use of specimens acceptable. NBAC sponsored a series of mini-hearings throughout the United States to assess the public’s attitudes about the use of specimens and the associated data for research (NBAC 1999). It reported that while the public expressed a wide variety of opinions, many thought that a general, one-time consent was sufficient. Other recent studies suggest that once they had given consent for their specimens to be used in a research study, many subjects did not think that additional consent was necessary for the specimens to be used in other research (McGuire et al. 2008; Trinidad et al. 2010; Vermeulen et al. 2009). However, additional research is needed to more adequately assess subject attitudes about the use of their specimens and data for research purposes.

Because the NCI/NAPBC model informed consent was developed prior to the issuance of the Privacy Rule (HIPAA), it does not include model authorization language for the use and disclosure of identifiable health information under the Privacy Rule. IRBs and researchers within covered entities will need to consider whether authorization is required for the use of any identifiable data that will be collected and, if so, whether a separate authorization should be obtained or the consent form modified to include the authorization.

Informed Consent for Use of Existing Collections.

There has been a great deal of discussion regarding the need for informed consent for the use of previously existing, archived collections of specimens and data. NBAC considered this issue in great detail and concluded that in most cases consent for the use of archived specimens could be waived, because much of this research would be minimal risk and it would be impracticable to meet the consent requirement for previously collected specimens (NBAC 1999). In many cases, the individuals from whom the specimens and data were collected are no longer living, and the informed consent requirements of the Common Rule do not apply. Other collections are anonymous or could be rendered anonymous, in which case consent would not be required. For identified specimens and/or data from living individuals, IRBs should consider whether a previous consent was obtained and, if so, whether the consent adequately covers the proposed research use. If no consent was obtained, the IRB could consider whether the requirements for a waiver of informed consent can be met or whether it would be appropriate to remove identifiers to render the specimens and/or data anonymous so that consent would not be required. If the IRB determines that subjects need to be

¹³ See http://www.cancerdiagnosis.nci.nih.gov/humanSpecimens/ethical_collection/brochure.pdf.

recontacted for a new consent, the IRB should consider what harms may be associated with recontact (e.g., invasion of privacy, anxiety).

Informed Consent for Secondary Use of Specimens.

Often, researchers wish to use specimens that were collected for one specific research project in another related or unrelated research project. The considerations for the IRB review of research involving the secondary use of specimens are similar to those described for existing collections. IRBs should determine whether consent was previously obtained and, if so, whether it covers the new research use. If the consent is not considered to be adequate for the new use the IRB could determine whether the research meets the criteria for a waiver of consent or a new consent is needed. If a new consent is needed, the harms associated with recontact to obtain it should be weighed. Researchers and their IRBs should think about the potential intended uses of specimens and include as much of this information as possible in the consent form at the time the specimen is obtained in order to simplify future decisions about the consent requirements for secondary uses.

Return of Research Results

The issue of if or when individual research results of studies involving specimens and the associated data should be returned to patients is the subject of considerable debate and is one that deserves particular attention. Much harm can result from the return of results with unclear meanings, results that have not been clinically validated, or results that are related to conditions for which no current treatment exists. In addition, it may be illegal under CLIA to provide test results for clinical care if the studies were not performed in a CLIA-approved laboratory. Although it may not be appropriate to return individual results to subjects, subjects may wish to receive general findings from the research on their specimens—for example, some researchers have provided general research reports to subjects through newsletters and Web sites. Researchers and repository managers should establish clear policies for the return of both individual research results and generalized findings at the outset of the research and, where appropriate, address these issues in the informed consent form. (See Chapter 24 for more information.)

In some cases an investigator who obtains specimens of coded private information about living individuals while conducting exempt research (under Category 4) may unexpectedly learn the identity of one or more living individuals. Or, for previously unforeseen reasons he or she might now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects under the regula-

tions. IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent under the regulations at §_____.116(c) or (d).

Unresolved Issues

There are numerous unresolved issues related to the collection, storage, distribution, and use of specimens and data for research. These include issues related to ownership, intellectual property, and benefit sharing in the context of research using human specimens and data. IRBs, investigators, and repository managers should check with appropriate regulatory and funding agencies and institutional legal offices regarding the status of these issues and the availability of any current guidance and/or policies in these areas.

E. Issues for Investigators: Practical Considerations for Researchers Establishing and Operating Human Specimen and/or Data Repositories

Early Planning

Researchers planning to establish a collection of specimens and/or data should consider a number of issues early in the planning stages, including the purpose and nature of the repository and anticipated future uses. Careful planning will allow subject consent forms to be made as specific as possible, minimizing the need to recontact subjects for future research projects. When specimens and data are collected from multiple collection sites, researchers may wish to obtain required human subjects assurances and institutional sign-offs as early as possible in the planning effort, because this process can be time consuming, particularly when foreign sites are involved. Researchers also should begin a dialogue with their IRB and institutional officials early during the protocol development in order to determine relevant institutional policies and procedures that must be followed and to avoid unnecessary problems and delays in the approval process.

Protocols for IRB Review

IRB review of the repository's operating procedures and policies is critical for the protection of donor subjects. Protocols for the establishment and operation of a human specimen and/or data repository should provide enough information to allow an IRB to assess compliance with the Common Rule, relevant medical records and privacy legislation, and state and local laws. The amount of information and level of detail required will vary depending on the size of the repository, the nature of the research, and the identifiability of the individuals from whom the specimens are collected. When specimens that

are collected for a specific research project also will be stored for future research, it is often desirable to submit separate IRB protocols for the research and the repository.

Research protocols for the collection of specimens and/or data should include details about the source of the specimens, how they were collected, what associated data are available, and whether they will be linked to subject identity. Information about whether consent was obtained and the type of consent that was obtained also should be provided. As noted in the section on IRB considerations, the return of individual research results involves considerable risks to subjects. Therefore, the protocol also should address the plans (if any) and policies of the repository for returning research results to subjects or their physicians.

Informed Consent Considerations for Researchers and Repository Managers

Researchers with repositories or specimens and/or data will need to consider whether informed consent will be required or whether it is appropriate to request a waiver of informed consent from the IRB. Another important factor to consider is the mechanism for tracking informed consent from the subjects from whom specimens and/or data are obtained. It may be necessary to track not only whether or not consent was obtained, but also to track when a “tiered” consent form such as the NCI/NAPBC model informed consent is used and for what types of studies consent was given (e.g., only research on cancer). Procedures should be established for dealing with withdrawal of consent after the specimens and/or data have been deposited in the repository or further distributed to researchers, and those procedures should be explained clearly in the consent form.

Repository Governance and Oversight

Systems for the governance of repository operation provide a mechanism for establishing policies and procedures to help make sure that specimens are appropriately used and that the rights and welfare of the subjects from whom the specimens and/or data are obtained are adequately protected. Approaches to consider include the use of steering committees or advisory boards that establish operating policies and procedures for the repository that include mechanisms for protecting subjects and maintaining privacy and confidentiality. Review processes should be established for requests for specimens and/or data to make sure that specimens and/or data are provided only for studies that are expected to contribute to scientific knowledge and that have the potential to improve the public health.

Privacy Considerations for Researchers and Repository

Managers

If the repository and/or researcher are part of a covered entity and private subject data are being collected, the Privacy Rule may apply. Researchers and repository managers need to consider how HIPAA will apply to their repository operations and/or the use of private subject data and whether a patient authorization is required (see Chapter 13). In addition, researchers may want to check with their IRBs and/or institutional legal counsel about whether other state and local laws related to privacy also may apply.

Whether HIPAA or other privacy regulations apply or not, research using human specimens and/or associated data should be designed in such a way that the risks to subject privacy and confidentiality are minimized. Repositories should establish operating procedures and policies that minimize these risks. It can be useful to look at the models for the protection of donor subjects that have been discussed in this Chapter. In general, it is advisable to store and distribute only those identifiers and/or identifiable private information that are needed for the anticipated research use. For example, in the honest broker model, the trustee removes identifying information before the specimens and/or data are sent to the researcher.

Unique code numbers unrelated to subject identities should be used whenever possible, and names or initials should not be included on specimen containers or released from the repository with associated specimens and/or documents. Storage of direct identifiers may be critical in some situations—for example, for long-term follow-up studies. However, it is advisable to avoid the use of direct identifiers such as name and Social Security number in routine analyses. When it is necessary to retain such direct identifiers, they should be securely stored and only accessible to a few authorized individuals who may be able to link them with the complete dataset. Encryption and other technology have been used to protect subject identity.

Employee confidentiality agreements provide another approach to protecting privacy and confidentiality. Repository employees sign agreements to protect confidential information such as patient names or other patient information and to use the data strictly for authorized repository activities. They are made aware that any disclosure to third parties or other misuse of the information is strictly prohibited.

Repository managers and/or researchers using specimens and/or associated data may want to consider whether it is appropriate to obtain a Certificate of Confidentiality, issued by the National Institutes of Health, to further protect subject confidentiality. Certificates of Confidentiality allow researchers to refuse to disclose identifying information on research partic-

ipants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that if disclosed could have adverse consequences for subjects or could damage their financial standing, employability, insurability, or reputation, and these certificates cover specimen and data repositories.¹⁴ Certificates of Confidentiality may not be appropriate for repositories for which informed consent has been waived because of the requirement that subjects be informed that a certificate of confidentiality has been obtained. Certificates of Confidentiality also do not apply to specimens and/or data that were collected prior to the issuance of the certificate.

Procedures and Policies for Distributing and Sharing Specimens and/or Data

Formalized procedures and policies for sharing specimens and/or data with other researchers can help to ensure that specimens and/or data from the repository are used appropriately and that subject privacy and confidentiality is maintained. As noted in the section for IRBs, the conditions under which specimens and/or data will be shared with other researchers should be clearly described in the informed consent under which the specimens and/or data were collected. Only those specimens and/or data that are necessary to achieve the research goals of the proposed study should be distributed by repositories. Many repositories have formalized review processes for specimen requests to help ensure that specimens are used appropriately. The proposed research use should be

consistent with the original informed consent under which the specimens and/or data were collected.

It is advisable for repositories, prior to providing specimens and/or data, to obtain an agreement from investigators that they will use the specimens and/or data only for the proposed research; follow applicable federal, state, and local regulations for the protection of human subjects; not try to identify the subject from whom the specimens and/or data were collected, and not share the specimens and/or data with third parties. Data use agreements, as described by the Privacy Rule, also may be required between the repository and the investigator. Some repositories require documentation of IRB review and approval from the investigator's IRB before specimens and/or data are distributed even though the identities of the subjects from whom the specimens are obtained may not be readily identified by the investigator. This review helps to make sure that the research is appropriate and consistent with the research use of the original informed consent under which the specimens and/or data are collected.

Other Information for Researchers and Repository Managers

The International Society for Biological and Environmental Repositories has developed a series of recommended best practices for human specimen repositories, including methods for protecting human subjects.¹⁵

¹⁴ Information on Certificates of Confidentiality is available at <http://grants.nih.gov/grants/policy/coc/index.htm>.

¹⁵ These best practices are available at www.isber.org.

Key Concepts: Research on Specimens, Data, Documents, or Records

- Risks of research using specimens and/or data must be balanced against the benefits anticipated from the research.
- Benefits from specimen research may include societal as well as psychosocial benefits to donor subjects. Risks from research on human specimens and/or data may include physical risks, the potential release or misuse of personal information and the potential misuse of research data.
- Most research on data, documents, records, or specimens may be considered minimal risk, although potential risks include physical risks and risks to privacy and confidentiality.
- Although the Common Rule and FDA regulations are the major federal legislation that governs the research use of specimens and data, other federal regulations and state and local laws also may be relevant .
- Consideration must be given to determining whether research proposals using human specimens and data meet the definition of human subjects research and if it is exempt from federal human subjects protection regulations. This determination should not be made by the PI.
- The requirements for informed consent for the use of specimens and/or data depend on a number of considerations, including whether the definition of a human subject has been met and whether specimens and/or data can be linked to living individuals. Unlinked or anonymized specimens and/or data are not subject to the Common Rule.
- The Common Rule at §____.116(d) allows waiver of informed consent if the research involves no more than minimal risk and meets certain other specified criteria. FDA regulations allow a waiver only under emergency circumstances.
- A consensus is emerging that, for prospectively collected identifiable specimens gathered during the course of routine medical care, consent beyond that contained in the general surgical consent is desirable. It is generally believed that consent for the collection, storage, and research use of specimens should be explicit and separate from the routine surgical consent.
- It may be appropriate to waive informed consent for the use of previously existing archived collections of specimens and data if the conditions for a waiver of consent are met. If a new consent is determined to be needed, the harms associated with re-contacting subjects should be considered.
- The Privacy Rule does not apply to specimens per se but may apply to identifiable subject data associated with the specimen. Repositories should consider how the Privacy Rule applies to their collections and whether HIPAA authorization is required from the subjects from whom the specimens and/or data are obtained. This authorization is distinct from the informed consent process.
- Careful consideration should be given to the issue of if or when individual research results should be returned to subjects. Harms may result from the return of results that have not been clinically validated, or conditions for which no current treatment exists.
- Repository operating procedures and policies should be designed to minimize risks to subject privacy and confidentiality. A number of models exist for the protection of subjects whose specimens and/or data are used by repositories.
- IRB review of the operating procedures and policies of repositories that contain identifiable specimens and/or data from living human subjects is critical for the protection of donor subjects.
- Formalized procedures and policies for sharing specimens and/or data with other researchers can help ensure that specimens and/or data from a repository are used appropriately and that subject privacy and confidentiality are maintained.

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Chapter 19

Ethical and Regulatory Issues in International Research

- A. Introduction
- B. Origins of the Current Ethical Debates
- C. The Evolution of International Ethical Standards
- D. U.S. Requirements in International Studies and Equivalent Protections
- E. Practical Challenges

Key Concepts

References

Appendix 19.A: Excerpts of OHRP Guidance for Nonlocal IRB Review



A. Introduction

U.S. Institutional Review Boards (IRBs) are confronted with more international protocols than ever before. These research projects often take place in countries and regions, and within socioeconomic, cultural, and political circumstances, that may be wholly unfamiliar to U.S. IRB members, particularly with respect to developing countries. Even for investigators with extensive experience in developing countries, the ethical issues can be complex. For bioethicists, the issues related to research ethics in developing countries have likewise been challenging but have also given rise to some important advances in thinking about research ethics and their role in the broader enterprise of protecting human subjects in research.

Although most of the controversy related to international research ethics relates to research conducted in developing countries, U.S. IRBs also review protocols describing collaborative, multicenter research projects with institutions in other developed countries, most notably Canada, Western European countries, Japan, Australia, and New Zealand. These countries have well-developed systems for protecting human subjects in research, but the designs and functions of these systems differ significantly from the U.S. regulatory approach. These differences are usually inconsequential for any given protocol, but on occasion they can result in

disagreements among U.S. IRBs and the Research Ethics Committees in the other countries.

One example is in the different approaches to compensation for injury sustained in research, for which some countries (Germany and France) require research sponsors to carry liability insurance, while other countries (United States and United Kingdom) have policies that are more case based and are often resolved through tort law. Another example is the dramatic difference among countries (and even among states within the United States) regarding the existence of mechanisms of legal protection for investigators studying behaviors that are either illegal or highly stigmatized socially. Thus, the availability of Certificates of Confidentiality in the United States, but not in another country, for example, may make certain collaborative research ventures difficult and may give rise to different risk assessments between the relevant U.S. IRBs and the collaborating IRBs or Ethics Boards.

Although social and behavioral research is an active area of global study, U.S. research institutions are also actively involved in international clinical trials. In September 2001, the Office of Inspector General (OIG) of the U.S. Department of Health and Human Services (DHHS) published *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*.¹ The report

¹ See www.vgtpce.gov.tw/~mre/goodexp/Fercap-Survey/OIG-Globalization-of-Clinical-Trials-Summary.pdf.

focused primarily on the Food and Drug Administration's (FDA's) approach to assuring human subjects protections in

The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects

the clinical trials that are the source of data for drug licensing applications in the United States. It highlighted the dramatic increase in foreign research activity over the past decade. The report documented a 16-fold increase in the number of foreign clinical investigators conducting drug research under FDA's Investigational New Drug (IND) Application procedures (from 271 in 1990 to 4,458 in 1999), and a three-fold increase in the number of countries hosting these trials (from 28 in 1990 to 79 in 1999). The countries with the greatest growth in drug trials also tended to be the least experienced in the conduct of clinical trials and therefore less experienced in the ethical review and oversight of these trials. In addition to China and Russia, these countries are located primarily in Central and Latin America, Eastern Europe and the Confederation of Independent States, and Africa. These findings led OIG to conclude that FDA cannot assure the same level of protections in foreign trials as in domestic trials.

This chapter provides an introduction to the kinds of issues encountered by investigators and IRB members when they engage in and review research that is conducted in other countries. It discusses issues that are germane to research conducted both in developed and developing countries. Since the health concerns faced by developing countries are enormous and likely pose the greatest challenges for the protection of human subjects in research, they are the main focus of the chapter.

B. Origins of the Current Ethical Debates

The principal concern for the United States about research conducted in developing countries relates to whether U.S. researchers and research sponsors exploit the citizens in those countries and whether the U.S. population at large unjustly benefits from research activities conducted in these countries. Debates arose in 1997 about what level of medical care must be provided to participants in clinical trials carried out in developing countries and funded by external donors. Other difficult issues have also arisen, such as what kind of obligations, if any, researchers or sponsors have with regard to providing medications to trial participants after the conclusion of a research study and whether there should be any plans on the part of researchers or sponsors to make successful trial products available more widely within host countries whose citizens were involved in clinical trials. These issues have generated extensive and sometimes bitter arguments and controversies and have been the subject of reports by national ethics commissions in the

United States and the United Kingdom (NBAC 2001; Nuffield 1999; Weijer and Anderson 2001).

The debate is important for two reasons. First, the concerns addressed in the debate are those that U.S. IRBs increasingly encounter. Second, under current U.S. regulations there is no direction or guidance about these issues. Therefore, IRBs are left with wide latitude for interpretation coupled with insufficient guidance about how to fulfill the letter and spirit of the U.S. regulations on some of the most difficult and important issues they currently encounter.

As with many policy-related crises, several high profile cases have been instrumental in fueling the debate. For example, the problem of "double standards" (that is, employing different ethical rules for studies conducted in developed and developing countries) emerged in the now famous placebo-controlled trials of zidovudine for the prevention of mother-to-child transmission of HIV in developing countries (Wilfert et al. 1999). These trials fueled the controversy and started a cascade of new guideline development (UNAIDS 2000), reconsideration and revision of existing international guidelines by the organizations that produce them (Levine 1999; Lurie and Wolfe 1997), and a number of reports and publications worldwide (NBAC 2001; Nuffield 1999). Into this mix, in December 2000, was added a six-part report in the *Washington Post*, entitled "The Body Hunters," that highlighted the idea of exploitation in international research to the American public, complete with first-hand accounts of research subjects and disturbing photographs of children living in dreadful conditions while acting as subjects in clinical trials in some of the world's poorest countries (Stephens 2000).

C. The Evolution of International Ethical Standards

Despite the increasing attention that has been devoted to international research ethics in recent years, there has been little explicit attention given to clarifying what is meant by ethical standards in this context. This is not simply an interesting philosophic question. Rather, it must be answered to gain clarity on the types of research design and practice that are ethically acceptable in different contexts and the mechanisms that can be put into place to ensure that these practices are carried out. Ethical standards are of two types, substantive and procedural.

Substantive Standards

Substantive standards are the principles and ethical commitments that form the underlying justification for specific rules, decisions, and judgments. There are essentially two types of challenges in the ethics of international

research: how to achieve some kind of workable consensus on what substantive requirements must be met and how to harmonize and, at times, simplify the various procedures that are meant to uphold these substantive standards. The procedural aspects of research oversight are made more complicated by the involvement of different legal authorities of the various nationalities participating in a given research project. Even when there is agreement about the ethical principles involved in protection of research subjects, legal standards differ among countries and often mandate different procedures. This is compounded in several developing countries by the absence of legal codes, regulations, or guidance and the lack of resources for developing them.

As discussed in Chapter 2, the *Declaration of Helsinki*, the *Nuremberg Code*, and the Council For International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving*

the Declaration of Helsinki, the Nuremberg Code, and the Council For International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects

Human Subjects (2002) are examples of substantive guidance, although in recent years these guidelines have been extensively debated. There is still considerable disagreement among experts and stakeholders regarding the extent and nature of ethical requirements that should be spelled out in these guidelines, such as the level of medical care to be provided to control groups in clinical trials and what kind of provisions or guarantees

of access to medications should be established for trial participants or others after a research study has ended. The use of placebo controls has also been debated. Supporters of placebo-controlled clinical trials conducted in populations with little access to best current treatment methods allege that research conducted with placebos would have more relevance for host country needs, because new interventions would be tested against the currently available care in the local setting.²

While making note of the arguments on both sides of the controversy, ethics committees must carefully consider the rationale for using placebos in localities where access to best methods is limited by economics or logistics.

Procedural Standards

Procedural standards describe ways in which substantive standards may, or should, be applied in practice. The Common Rule provides largely procedural guidance, in that it describes specific conditions and steps that should be taken within human research protection programs (HRPPs) to ensure the appropriate conditions for independent review by an IRB. The Common Rule requirements are also substantive to the extent that they describe specific ethical commitments, for example, that the risk to human subjects must be minimized and that when they have been minimized they must be justified on the basis of the prospect of personal benefit to the human subjects, social value, or both (§____.111).

Other procedural guidelines have become increasingly important in international research. The International Conference on Harmonisation *Good Clinical Practice: Consolidated Guidance* (ICH-GCP guidelines) (ICH 1996) are a set of procedures thought to be constitutive of good—that is, ethical, effective, high quality and safe—clinical practice in the course of clinical drug trials.³

The International Conference on Harmonisation Good Clinical Practice: Consolidated Guidance

The ICH-GCP guidelines represent an attempt by the pharmaceutical industry in the United States, Western Europe, and Japan to establish a common set of practices that, when followed, would satisfy the ethical and practical requirements of drug and device regulatory authorities in the participating countries.⁴ The guidelines, which are recognized by FDA, constitute an important development for FDA, particularly because standardizing processes in clinical trials is expected to reduce the prevalence of clinical trial practices that give rise to poor data, greater risk to research subjects, and other ethical violations. Because guidances are not regulations or laws, however, they are not enforceable, either through administrative actions or through the courts. Although the ICH-GCP guidelines have not been adopted universally to date, they have generated significant interest from other countries and appear to have the potential to emerge as a unifying framework for industry-sponsored drug and device trials.

Another new and important set of guidelines is the *Operational Guidelines for Ethics Committees That Review Biomedical Research*, produced by Tropical Disease

² See www.wma.net/e/policy/b3.htm, paragraph 29; www.wma.net/e/policy/b3.htm, note of clarification to paragraph 29.

³ See www.fda.gov/cder/guidance/959fnl.pdf.

⁴ The six ICH sponsors are the European Commission, European Federation of Pharmaceutical Industries Associations, Japanese Ministry of Health and Welfare, Japanese Pharmaceutical Manufacturers Association, Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and Pharmaceutical Research and Manufacturers of America.

Research (TDR) Unit, an independent affiliate of the World Health Organization (WHO) (WHO 2000). The guidelines represent an important contribution to the evolving battery of

**Operational
Guidelines for
Ethics Committees
that Review
Biomedical
Research**

international standards. As procedural standards, they aim to assist ethics committees, primarily in developing countries, in establishing procedures and policies. They arise from TDR Unit's accumulated experience in developed countries and the growing recognition of the need for local capacity for independent review. The procedures are offered to help promote competence, comprehensiveness, and consistency in ethical review.

In general, there continues to be some uncertainty about how effectively the substantive ethical standards (i.e., the protection of human subjects) are achieved in practice. Moreover, procedural standards in developing countries may be different from those set out in the Common Rule. Further effort may be required in some cases to promulgate the standards and ensure that they become part of the culture of ethical conduct in research (Lavery 2001). However, it is important to avoid the uncritical presumption that the U.S. system uniformly results in greater protection than that provided by systems in other countries.

For the most part, discussion about standards in international research ethics continues to focus on the wording of guidelines and popular codes of conduct, such as the *Declaration of Helsinki* and the CIOMS guidelines. But there are several important reasons why these guidelines might be considered insufficient, on their own, as global standards. First, since the concept of a standard implies at least some moderate level of uniformity, it is critical to recognize that the current international guidelines diverge on important substantive issues, such as the appropriate use of placebo controls in clinical trials, what should constitute benefits to research subjects, and what are appropriate obligations for researchers, sponsors, and host country governments and agencies at the end of research studies, particularly those testing prophylactic, diagnostic, or therapeutic interventions.

Second, the guidelines use different language and justifications, although in general they support the same substantive commitments. Third, these guidelines pursue different goals and offer guidance to different constituencies. The *Declaration of Helsinki*, for example, is produced by the World Medical Association (WMA), an international organiza-

tion of medical associations that represents the views and interests of physicians around the world. WMA broadened its target audience for the first time in its 2000 revision by stating that it provides guidance to physicians *and other participants* in medical research. The CIOMS guidelines, on the other hand, came into being in the late 1970s "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the *Declaration of Helsinki*, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements."⁵

Fourth, the various guidelines make different claims of authority, perhaps the boldest of which is presented in the 2000 revision of the *Declaration of Helsinki*, which states that "(n)o national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration" (WMA 2002, para. 5). In fact, the status of the *Declaration of Helsinki* and other international guidelines is not clearly established in international law, marking yet another reason for skepticism about their functioning, on their own, as truly global standards. Finally, many existing guidelines are written for a specific type of research, such as clinical drug trials (ICH-GCP guidelines), HIV vaccine trials (UNAIDS), HIV prevention research (HIV Prevention Trials Network (HPTN)), or epidemiological studies (CIOMS). As such, their function as standards is, at best, fragmentary.

However, it is important to recognize that many of the ethical concerns regarding the treatment of subjects in international research are similar to those raised in conjunction with research conducted in the United States. They include choosing the appropriate research question and design, ensuring prior scientific and ethical review of the proposed protocol, selecting subjects equitably, obtaining voluntary informed consent, and providing appropriate treatment to subjects during and after the study. These concerns are consistent with principles endorsed in many international research ethics documents. For example, various descriptions of the process and nature of informed consent can be found in the Common Rule (§___116 and ___117); FDA regulations (21 CFR 56); CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993); *ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice (GCP)* (1996); and WMA's *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (2000).

⁵ See www.cioms.ch/guidelines_nov_2002_blurb.htm.

D. U.S. Requirements in International Studies and Equivalent Protections

As described in Chapter 3, there are three primary sources of federal regulatory protection for human subjects: DHHS regulations for the protection of human subjects, codified at 45 CFR part 46 and including Subparts A through D;⁶ the Common Rule, codified by 17 executive branch departments and agencies, which is identical to Subpart A of 45 CFR 46 above;⁷ and FDA Informed Consent and Institutional Review Board regulations at 21 CFR Parts 50 and 56.⁸

These regulations are relevant to international research conducted by U.S. investigators working abroad, that is, research that is conducted or supported by one of the U.S. federal departments and agencies that have adopted the Common Rule or are regulated by FDA but that is conducted in another country.⁹ The Common Rule at §____.101(a) makes it clear that the policy applies to “research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.” However, the regulations allow for differences that might exist between U.S. and foreign applications of the regulations. The Common Rule at §____.101(h) states as follows:

When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly [sic] Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy...

The Common Rule at §____.101(g) also emphasizes that the policy “does not affect any foreign laws or regulations

which may otherwise be applicable and which provide additional protections to human subjects of research.”

Approvals of the substitution of the foreign procedures are to be published in the *Federal Register* (or elsewhere, as provided for in department or agency procedures). (Note that FDA has not adopted this provision for research that it regulates. All FDA-conducted or supported research, however, must comply with both DHHS and FDA regulations [see below].)

The current procedure for approving DHHS-supported research with a foreign component begins with the domestic institution with which the U.S. investigators are affiliated if the award is made to the U.S. investigator rather than to a foreign scientist. If the U.S. institution has an approved assurance on file with DHHS or another federal department or agency subscribing to the Common Rule that covers the research to be supported or conducted, the proposed research must be reviewed and approved by the institution’s IRB before funding is provided, as with any research involving human subjects. If DHHS supports the research, each foreign institution should, upon request, submit an appropriate assurance to the Office for Human Research Protections (OHRP). Because, at the present time, no international code prescribes exactly the same procedures for protecting human subjects as the U.S. regulations, OHRP reviews the actual procedures detailed by the foreign institution as the primary basis for negotiating acceptable assurances. International codes are, however, taken into consideration in the negotiations. Under the terms of the assurance,¹⁰ any one of five existing ethical guidelines may be used by the foreign institution: the U.S. Common Rule, the *Declaration of Helsinki*, ICH-GCP guidelines, *Canadian Tri-Council Policy Statement on Ethical Conduct for Research*, or *Indian Council of Medical Research Ethical Guidelines*. In addition, other guidelines may be used if recognized by a U.S. department or agency that has adopted the Common Rule. Along with filing an assurance with OHRP, foreign institutions involved in collaborative research that receives U.S. government support need to register an Ethics Review Board or IRB with OHRP. If the institution’s practices differ from those in the U.S. regulations, OHRP can require that particular procedures be followed as a condition of the assurance.

The U.S. Agency for International Development (USAID), which supports research conducted abroad, provides additional guidance for determining which parties must be

⁶ See www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

⁷ See www.access.gpo.gov/nara/cfr/waisidx_01/45cfr46_01.html.

⁸ See www.access.gpo.gov/nara/cfr/waisidx_01/21cfr50_01.html and www.access.gpo.gov/nara/cfr/waisidx_01/21cfr56_01.html.

⁹ There are also other discretionary standards that impose additional requirements to those of the Common Rule and FDA regulations. A specific example with particularly high relevance for international research is the Department of Defense regulation 10 USC 980, which requires that there must be intent to benefit subjects in research if they are unable to provide consent.

¹⁰ See www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm.

involved in either an assurance or a review. For example, USAID guidance states that “the mere fact that research occurs at a certain place (such as a health department, school or supermarket) does not mean that ‘place’ would be considered a research institution. If a site is only opening its doors to researchers or data abstractors, or is merely providing data, it is not considered a research institution.”¹¹ USAID guidance suggests that one mechanism for clarifying responsibility is a “cooperative amendment to assurances of institutions participating in cooperative research, which can be agreed to by those institutions, and approved by the sponsoring agency to document the terms of reliance on another institution’s IRB.”¹²

If the U.S. institution holds an assurance, but the research is supported by a non-DHHS source, DHHS has less authority in review of the protocols for human subjects protections. Rather, as required by §___,103, the assurance-holding institution retains responsibility for protecting the rights and welfare of all human subjects involved in research under the institution’s auspices. The current OHRP assurance mechanism gives institutions the option of declaring that the assurance will cover only DHHS-funded research, or research funded from all sources. In this way, the assurance mechanism (the institution’s legal promise of compliance) has been used to effectively expand the reach of the Common Rule regulations to research conducted with nonfederal sources, or private sources.

Departments and agencies other than DHHS follow different procedures for reviewing and approving research with foreign components. IRBs should consult the particular department or agency involved.

Assurances for Non-U.S. Institutions

Non-U.S. institutions engaged in human subjects research that is conducted or supported by DHHS also must submit an assurance to OHRP for approval. The institution’s Assurance Signatory Official must be authorized to represent and commit the entire institution and all of its components to a legally binding agreement.

The non-U.S. institution must designate the IRBs/Independent Ethics Committees (IECs) of record for this

assurance and ensure that all designated IRBs/IECs are registered, or are in the process of registering, with OHRP prior to submitting the assurance application. To determine if an IRB/IEC is registered with OHRP, institutions can check the OHRP Web site.¹³ If the institution relies on another institution’s IRB/IEC, this arrangement must be documented in writing between the two institutions. The agreement must be kept on file at the institutions and be available for review by OHRP upon request, but it should not be submitted with the Federalwide Assurance (FWA) application.

Determination of Equivalent Protections

In contrast to requirements for foreign institutions to follow U.S. policy guidelines regarding human subjects protections, the phrase “equivalent protections,” derived from the regulatory language cited above,¹⁴ refers to the potential for U.S. government agencies to recognize foreign regulations, policies, or procedures in lieu of the Common Rule.

The phrase *at least equivalent* in the regulatory language has been the focus of some discussion in recent years, as investigators, IRBs, HRPPs, and OHRP try to sort out how such a determination can be made and by whom. In the case of DHHS, any formal determination of equivalent protections would be made by OHRP. The current OHRP position is that the broad policy outlines of international standards, such as the *Declaration of Helsinki* or the *Nuremberg Code*, are a starting place for determining equivalency but are not sufficient. The FWA, which is currently the main instrument by which assurances are made with OHRP (see Chapter 5), already performs the assurance function with foreign institutions, although a formal comparison of protections in the way described in the regulations is not conducted under the current scheme. To truly make a determination of equivalency, OHRP would have to compare the protections provided by the institution’s procedures with those required by the Common Rule. If such equivalency were to be found, then the department or agency head could approve the substitution of those procedures in lieu of those of the Common Rule.

Debates have focused on whether the equivalency determination should primarily rest on substantive requirements, procedural requirements, or some combination of both. Certainly the reference to “procedures” at §___,101(h) repeats the policy’s recognition that “procedures normally followed” in foreign countries “may differ from those set forth in this policy.” This has led some to believe that determinations of equivalent protections should be focused only on

¹¹ See www.usaid.gov/our_work/global_health/home/TechAreas/commrule.html.

¹² Ibid.

¹³ See <http://ohrp.cit.nih.gov/search/asearch.asp>.

¹⁴ §_46___,101(h).

matters of institutional review procedures (for example, where the equivalent structure and functioning of an IRB are required).

In a background paper prepared for NBAC's 2001 report, Bernard Dickens points out that while the U.S. federal regulations are largely procedural in nature, §___101(h) cites the *Declaration of Helsinki* as the type of guideline that might satisfy the requirements of equivalent protections. Dickens concluded that "equivalence addresses substantive principles of ethical conduct of research with human subjects, and not only the process of review itself" (Dickens 2001, A3). He goes on to examine how these substantive principles might be satisfied through competent research ethics review, using procedures that differ from those provided in the U.S. federal regulations.

Thus, substantive ethical principles or standards are more fundamental and, therefore, much less subject to negotiation than are matters of procedure. Any given set of substantive ethical standards and principles may give rise to more than one set of appropriate procedures to implement these standards. As long as a particular procedure (e.g., obtaining informed consent without documenting signatures) is consistent with the ethical standard, it should be seen as less consequential. In contrast, disagreements or tensions regarding a substantive ethical principle or standard can cause problems for which no mere procedural solution would be adequate. Noting this, NBAC recommended that "the U.S. government should identify a set of procedural criteria and a process for determining whether the human participants protection system of a host country or a particular host country institution has achieved all the substantive ethical protections" that the NBAC report described (2001, 89).

In its 2001 report, *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*, the DHHS OIG also recommended that OHRP exert leadership in developing strategies to ensure that adequate human subject protections are afforded for non-U.S. clinical trials regardless of the source of U.S. funding for the trials. The OIG report stated that

...it could be particularly helpful for the Office for Human Research Protections to address how the Department can better assess whether other nations' laws and practices afford equivalent protections to those that apply to human subjects participating in clinical trials in the U.S. We recognize the sensitivities and complexities associated with such guidance,

but the matter appears to warrant serious consideration (21).

In July 2003, an Equivalent Protections Working Group formed by OHRP issued a draft report suggesting a framework by which criteria may be developed for determinations of equivalent protection. Currently, the working group recommendations are still being considered and are being reviewed by federal agencies to determine the next steps for implementing a process for evaluating human subjects protections according to an equivalent protections framework. The report outlines the following procedural issues:

- steps in determining equivalence
 - articulation of the specific protections embodied in 45 CFR 46
 - assessment of the protections provided by the institution's procedures
 - comparison of the protections provided by the institution's procedures with those provided by 45 CFR 46 and determination of equivalence, or not
 - approval by the relevant department or agency head for the substitution of the institutional procedures in lieu of the procedures of 45 CFR 46
- mechanism of assurance with OHRP
 - assurance from the institution that the substituted procedures will be followed in the conduct of DHHS-supported¹⁵ human subjects research to be completed and filed with OHRP

To clarify the scope of the equivalent protections provision, the working group attempted a careful characterization of what protections may be reasonably inferred from the content of the Common Rule. It drew two general conclusions: (1) that the primary focus of the Common Rule is the accountability of the research institution for the welfare and rights of research subjects and (2) that the overarching goal of the specific accountability mechanisms and procedures described in the Common Rule is to establish expectations of ethical conduct within the research institution. The working group concluded, therefore, that the protection of the welfare and rights of human subjects of research is achieved as much through the proper promotion and conscientious execution of standard practices and procedures within the institution as through competent reasoned application of ethical principles in research ethics review. The working group concluded that adequate protections require that three main levels of responsibility are recognized and met: (1) responsibilities of

**establish
expectations of
ethical conduct**

¹⁵ The current assurance process employed by OHRP permits institutions to decide whether the assurance covers only DHHS-funded research or is extended to all human subjects research conducted within the institution.

the institution; (2) responsibilities of the IRB; and (3) discretion on the part of the appropriate U.S. department or agency head to take action, where necessary, to ensure that the responsibilities are appropriately exercised.¹⁶

FDA Acceptance of Foreign Clinical Studies

FDA may accept clinical studies conducted outside the United States in support of safety and efficacy claims for drugs, biological products, and medical devices. All drug, biologic, and device studies conducted under an IND Application or Investigational Device Exemption (IDE) are governed by the FDA informed consent and IRB requirements.¹⁷ In general, studies conducted in the United States involving new drugs or devices are carried out with INDs and IDEs, respectively. However, in foreign countries, there is no FDA jurisdiction regarding testing of drugs or devices in human subjects. FDA authority over research conducted in foreign countries is limited to its authority to accept or reject data in support of U.S. licensing of products that have already been tested.

Currently FDA will accept a foreign clinical study involving a *drug or biological product* not conducted under an IND only if the study conforms to whichever of the following provides greater protection of the human subjects: the ethical principles contained in the 1989 version of the *Declaration of Helsinki*, the ICH-GCP guidelines, or the laws and regulations of the country in which the research was conducted.¹⁸ The reader is advised to check on the status of this policy, because it is being reconsidered by FDA.

In parallel language, FDA will accept a foreign clinical study involving a *medical device* not conducted under an IDE only if the study conforms to whichever of the following provides greater protection of the human subjects: the ethical principles contained in the 1983 version of the *Declaration of Helsinki* or the laws and regulations of the country in which the research was conducted.¹⁹

In addition to recommending better procedures for determining equivalent protections, the 2001 DHHS OIG report also recommended that FDA enhance protections for human subjects in foreign trials by improving the capacity of foreign committees, by encouraging promises of compliance from foreign investigators and improved site monitoring, and by developing an improved database for tracking foreign research activities by location (DHHS OIG 2001).

E. Practical Challenges

Although IRBs and investigators should assume that the regulations have legal force when applied in other countries, precisely how the regulations are meant to function remains somewhat unclear (DuBois 2003). The process of negotiating institutional assurances with OHRP (see Chapter 5), which are required of foreign institutions receiving U.S. federal funding, and the detailed procedural requirements of research ethics review, in particular, are seen by some as tedious and of dubious value for the protection of human subjects (NBAC 2001). Some researchers express a preference for developing international standards as a way of maintaining the strong ethical commitments found in the U.S. regulations but avoiding the perception that the United States is too forceful in imposing its own particular standards and practices. For example, according to a 1997 survey of international researchers holding Single Project Assurances, “there needs to be an increased acceptance by [OPRR] of ethical guidance and standards of practice in other countries” (Wichman et al. 1997, 5).

Clearly, challenges are different for researchers conducting studies in other developed countries—for example, multisite clinical drug trials conducted simultaneously in the United States, Canada, and Europe—than they are for studies conducted in Sub-Saharan Africa, for example. Although the general issues are similar for both, the concerns about research conducted in developing countries have received the most attention.

IRB Considerations

Beyond the procedural considerations of ethics review of international studies (which have to be managed through the process described above), current regulations require that each institution adopt a set of ethical principles that should guide its research and research ethics review practices. Although it is not specified in the regulations, it is assumed that the guiding ethical principles should be consistent with the ethical principles outlined in the *Belmont Report* (National Commission 1979) and numerous other international guidelines and standards.

Problems of interpretation and application of guidelines exist for researchers and ethics review committees in both developed and developing countries. Some problems regarding informed consent are particularly difficult when the detailed procedural requirements of the U.S. regulations are unfamiliar to, or otherwise inconsistent with, the cultural values and ethical commitments of the host country. It is

¹⁶ In March 2005, OHRP requested public comments on the working group draft; see www.hhs.gov/ohrp/international/EquivProtectNotice.pdf.

¹⁷ 21 CFR part 312 IND regulations and 21 CFR part 812 IDE regulations.

¹⁸ 21 CFR 312.120(c)(1).

¹⁹ 21 CFR 814.15(a) and (b).

important, therefore, for U.S. sponsors of international research to address issues concerning the application of U.S. research regulations for informed consent in settings with different cultures and customs. It also is critical that IRBs or their equivalents are sensitive to several issues that can arise, such as the following:

- Do cultural factors create a barrier to complying with the substantive ethical standard of informed consent, and is it permissible to depart from that standard if the research could not otherwise be carried out?
- How should investigators obtain voluntary informed consent in settings in which the belief system of potential research participants does not explain health and disease using the concepts and terms of modern medical science and technology?
- How can voluntary participation be ensured in settings in which community leaders may exert pressure on the entire community to enroll in a proposed study?
- How can cultural differences be addressed that make it difficult or impossible for other countries to adhere to U.S. federal regulations stipulating specific procedures for obtaining voluntary informed consent?
- How might the United States modify its informed consent regulations to adapt to various cultural circumstances in other countries without compromising the substantive ethical standard of informed consent? (NBAC 2001)

Without a doubt, acknowledging and incorporating cultural diversity in the review process remains a challenge.

acknowledge and incorporate cultural diversity in the review process

Ideally, each IRB that reviews international research should include at least one person with international experience; however, this currently appears to be an optimistic goal. Thus,

one of the main challenges for addressing the ethics and regulation of international research successfully in the United States is to find ways of overcoming the general lack of knowledge about conditions in other countries, particularly developing countries, where conditions can be the most impoverished and challenging.

One way in which IRBs can address this problem is through the use of consultants as allowed by the Common Rule. IRBs may look for a member of the local community with experience in the country where the research will take place, or they may find a consultant in the host country who is able to review the research and provide recommendations. The use of such consultants does not require the IRB to

amend its roster or FWA, and the consultant does not need to be present at the meeting for his/her opinions to be considered.

IRB members face an enormous test in determining whether local conditions are ever relevant in the application of ethical principles and regulations, a point that has begun to draw some focused attention recently (Fidler 2001). Although, technically, the Common Rule does not permit any special accommodations resulting from local conditions and circumstances, some of the basic responsibilities of IRBs, such as weighing the risks and benefits of a given study, require a clear account of what is at stake, for whom, and what circumstances might have a bearing on the IRB's judgment.

Local laws, institutional policies and constraints, professional and community standards, and population differences are examples of pertinent local factors that can influence the setting of research (§____.107(a)). The spirit of the regulations certainly emphasizes the importance of local review. However, local review by an IRB or equivalent may not be available for research conducted in developing countries. In these cases, if the research is to proceed it might be necessary to rely on the review of an IRB distant from the location in which the research is to be conducted and/or to become more innovative in arranging and managing local review.

The Common Rule and FDA regulations allow the review of research by IRBs in locations other than where the research is to be performed (e.g., through an independent or noninstitutional IRB), although federal departments and agencies have the discretionary authority to prohibit this practice. Therefore, an IRB may review studies that are not performed onsite as long as the regulatory requirements are met. However, when nonlocal IRB review takes place, the reviewing IRB must document its role and responsibilities. FDA expects that a written agreement will be executed between the performance site where the research is to be conducted and the IRB or its institution. The agreement should confirm the authority of the IRB to oversee the study. Although the IRB assumes responsibility for oversight and continuing review, the clinical investigator and the research site retain the responsibility for the conduct of the study. OHRP also has procedures and guidance for approving nonlocal IRB review of research (see Appendix 19.A).

The U.S. IRB should review all active or proposed international research approved at the facility to determine the degree of oversight being exercised by the U.S. investigator. In general, when reviewing international research, the

IRB should obtain from the investigator or elsewhere the following explicit information:

- Information about the entities at the local site that are overseeing the research and their ability to follow through in addressing human research protection issues:
 - Is there an FWA in place under OHRP?
 - Are there local ethics committees or IRBs in place to oversee the research?
 - If there is more than one IRB, how will the IRB or investigator assure coordination of IRB groups?
 - What national or international standards are used to protect subjects?
 - Who will follow up if there is noncompliance or a protections problem?
- Copies of the protocol and informed consent document in English and in the language of the country where the research is to take place.
- A clear explanation of the recruitment and consent processes involved.
- Information about the endorsement and accountability of the institution(s) of the foreign collaborators, if there are any.
- An assurance that research procedures are compatible with local laws and regulations.

Two areas of effort would improve the review process for studies conducted in developing countries. First, training, education, and capacity-building efforts targeted to countries where DHHS-supported research is currently being conducted and where current research ethics review practices and infrastructure are underdeveloped would enhance the capacity of local sites to protect human subjects in research. Simultaneously, education and training must continue to identify creative ways to improve the knowledge and experience of U.S. IRB members regarding conditions and cultures in developing countries.

Ethical standards in international research are particularly challenging because of the overlay of all the complexities of research ethics on a contextual background that includes poverty, lack of medical care, and complex social and political conditions. International ethical standards are evolving, as they should, in response to changing political sensibilities and growing awareness of the depth of economic and health crises in the developing world. Therefore, it is critical for ethics review committees, researchers, sponsors, and other concerned parties to engage in thoughtful and open discussion regarding unresolved issues. There are no easy formulas for determining what is ethical in this complex arena; continued dialogue and investigation of ethical dilemmas are required. As the field of international research ethics gains maturity, more refined guidance can be developed with the aim of continuing to advance health research to benefit global health while maintaining high ethical standards.

Key Concepts:

Ethical and Regulatory Issues in International Research

- The Common Rule provides overall although not exclusive procedural guidance regarding ethical and regulatory issues in international research, because it describes specific conditions and steps that should be taken within HRPPs. These regulations are relevant to international research conducted by U.S. investigators working abroad—that is, research that is funded either with U.S. federal funds or with private funding but that is conducted in another country. Procedural standards in developing countries may be different from those set out in the Common Rule.
- The *Declaration of Helsinki*, the *Nuremberg Code*, and the CIOMS guidelines are examples of substantive guidance. The ICH-GCP guidelines provide a set of procedures that are thought to be constitutive of good clinical practice—that is, ethical, effective, high-quality, and safe—in the course of clinical drug trials.
- Many of the ethical concerns regarding the treatment of subjects in international research are similar to those raised in conjunction with research conducted in the United States. They include choosing the appropriate research question and design, ensuring prior scientific and ethical review of the proposed protocol, selecting subjects equitably, obtaining voluntary informed consent; and providing appropriate treatment to subjects during and after the study.
- When research covered by the Common Rule takes place in foreign countries, procedures normally followed in those countries may differ from the procedures set forth in this policy. In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided by the Common Rule, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements of the Common Rule.
- The current procedure for approving DHHS-supported research with a foreign component begins with the domestic institution with which the U.S. investigator(s) are affiliated. If the U.S. institution has an approved assurance on file with DHHS, the proposed research must be reviewed and approved by the institution's IRB before submission for funding, as with any research involving human subjects.
- If DHHS funds the research, each foreign institution should, upon request, submit an appropriate assurance to OHRP. Because currently no international code prescribes exactly the same procedures for protecting human subjects as those prescribed by the U.S. regulations, OHRP reviews the actual procedures detailed by the foreign institution as the primary basis for negotiating acceptable assurances. International codes are, however, taken into consideration in the negotiations. If the institution's practices are not equivalent to the U.S. regulations, OHRP can require that particular procedures be followed before recommending approval of the substitution.
- Departments and agencies other than DHHS follow different procedures for reviewing and approving research with foreign components. IRBs should consult the particular department or agency involved.
- FDA may accept clinical studies conducted outside the United States in support of safety and efficacy claims for drugs, biological products, and medical devices. All drug, biologic, and device studies conducted under an IND or IDE are governed by the FDA informed consent and IRB requirements (21 CFR Part 312 [IND regulations] and 21 CFR Part 812 [IDE regulations]).
- When studies are conducted in developing countries, additional considerations might pertain, especially with regard to the informed consent process.
- The Common Rule and FDA regulations allow review of research by IRBs in locations other than where the research is to be performed (e.g., independent or noninstitutional IRB). Agencies and departments have the discretion to prohibit this practice as appropriate.

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Appendix 19.A: Excerpts of OHRP Guidance for Nonlocal IRB Review

Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved assurance possess sufficient knowledge of the local research context to satisfy these requirements. This responsibility endures regardless of the IRB's geographic location relative to the institution and the research. It is particularly critical where the research involves greater than minimal risk to subjects or vulnerable categories of subjects.

- (A) OHRP considers the following standards when evaluating the adequacy of IRBs designated under an institutional assurance, particularly when the IRBs are geographically removed from the local research context. These standards reflect minimum levels of adequacy. More stringent standards may be required, depending upon the nature of the proposed research or the relevant research context.
- (1) Where the research involves minimal risk to subjects, the IRB should demonstrate that it has obtained necessary information about the local research context through written materials or discussions with appropriate consultants.
 - (2) Where the research involves greater than minimal risk to subjects but
 - (a) the local research context involves no intervention or interaction with subjects and
 - (b) the principal risk associated with the local research context is limited to the potential harm resulting from a breach of confidentiality, the IRB should
 - (c) demonstrate that it has obtained necessary information about the local research context through written materials or discussions with appropriate consultants; and determine and specifically document that provisions to protect the privacy of subjects and maintain the confidentiality of data are adequate.
 - (3) Where the research involves greater than minimal risk to subjects and item (A)(2) does not apply, the IRB should demonstrate that it has obtained necessary information about the local research context through one or more of the following mechanisms, or through other mechanisms deemed appropriate by OPRR for the proposed research and the local research context.
 - (a) Personal knowledge of the local research context on the part of one or more IRB members, such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community.
 - (b) Participation (either physically or through audiovisual or telephone conference) by one or more appropriate consultants in convened meetings of the IRB. Such consultant(s) should have personal knowledge of the local research context, such knowledge having been obtained through extended, direct experience with the research institution, its subject populations, and its surrounding community.
 - (c) Prior written review of the proposed research by one or more appropriate consultants (see (b) above), in conjunction with participation (either physically or through audiovisual or telephone conference) by the consultant(s) in convened meetings of the IRB, when such participation is deemed warranted either by the consultant(s) or by any member of the IRB.
 - (d) Systematic, reciprocal, and documented interchange between the IRB and elements of the local research context. Such interchange should include (i) periodic visits to the research site, occurring several times per year, by one or more IRB members in order to obtain and maintain knowledge of the local research context, including the research institution, its subject populations, and its surrounding community; (ii) periodic discussion with appropriate consultants knowledgeable about the local research context; (iii) regular interaction with one or more designated institutional liaisons; and (iv) review of relevant written materials.

(Continues on following page)

Appendix 19.A: Excerpts of OHRP Guidance for Nonlocal IRB Review

- (B) Regardless of the IRB's geographic location, each institution holding an OPRR-approved Assurance is expected to maintain a unified system of protections applicable to all human subjects research covered under the Assurance.
- (1) Each institution remains responsible for safeguarding the rights and welfare of human subjects within its local research context.
 - (2) Each institution remains responsible for educating the members of its research community in order to establish and maintain a culture of compliance with Federal regulations and institutional policies relevant to the protection of human subjects.
 - (3) Each institution remains responsible for implementation, within its local research context, of appropriate oversight mechanisms in order to ensure compliance with the determinations of the reviewing IRB.
 - (4) Where institutions holding an OPRR-approved Assurance engage a separate entity to perform human subject protection activities, OPRR must review and approve those portions of the contract and/or other clarifying documentation detailing responsibilities and implementation mechanisms relevant to such activities.
 - (a) Such documentation must specify mechanisms to ensure that all institutional responsibilities under the Assurance are fulfilled (e.g., procedures for retention and accessibility of records in accordance with DHHS regulations at [45 CFR 46.115](#); procedures for prompt reporting to the IRB of proposed changes in approved research and for prompt reporting to OPRR of unanticipated problems in accordance with DHHS regulations at [45 CFR 46.103\(b\)\(4\), \(5\)](#)).

Chapter 20

Workers as Research Subjects

- A. Introduction
- B. What Is a Worker Study?
- C. Workers as a Vulnerable Population
- D. Genetic Information in Worker Studies
- E. Considerations for Institutional Review Board Review
- F. Criteria for the Informed Consent Process and Documentation
- G. Expectations of Privacy and Confidentiality
- H. Other Stakeholder Interests

Key Concepts

References



A. Introduction

Workers can become the subjects of research when they are recruited, for example, to test new nonmedical products and equipment, complete behavioral surveys, enroll in workplace health effect studies, or provide blood samples for genetic studies to monitor susceptibility to certain workplace toxins. Research with this class of human subjects can become an even greater challenge when the workers are the focus of research through circumstances beyond their control, such as when they are exposed to potential hazards in the workplace. In these circumstances, the ethical dilemma that requires careful consideration is the balancing of

paycheck vulnerability

the common good that can be gained from such studies with the rights and autonomy of the individuals involved, not only as workers but also as people. A primary concern is that workers not be coerced or unduly influenced to participate in studies because they fear for their jobs or positions in the workplace. These concerns can create vulnerability, perhaps best termed as *paycheck vulnerability*, that requires special scrutiny on the part of Institutional Review Boards (IRBs).

The ethical principles that provide the framework for the Common Rule are applicable when research is conducted in the workplace. To assure respect for persons, the Common Rule requires that each research subject give voluntary informed consent to his/her participation in a study. For

consent to be informed, subjects must have adequate and understandable descriptions of the study purpose, know what is expected of them, and be informed of any benefits and/or risks they may experience. For consent to be voluntary, they must not face coercion regarding enrollment, reprisal for their decisions, or loss of benefits from their study results. The principle of beneficence can be addressed by providing a health benefit to the worker or a promise of detecting medical conditions, by improving health/quality of life, by providing safer working conditions, or by establishing entitlement claims. For worker-subjects, justice includes allocation of resources and equitable choice of and fairness to subjects, both potential and enrolled. Nonmaleficence implies doing no harm and includes protection from loss of job, insurance, or privacy. Historically, these expectations have not been explicitly addressed in workplace research; however, some employers in the private sector, especially where hazardous materials are used or liability issues prevail, have voluntarily adopted scientific and human subject review systems.

Previous chapters in this resource manual have discussed the meaning of research within the context of the Common Rule, which becomes less clear in certain occupational contexts—for example, identifying the best safety gear for firefighters or ergonomic studies of office workers. Confusion about the applicability of federal regulations can arise when workers are asked to participate in a health study while on the job, because such a study can raise conflicting

interpretations of its intended benefits and possible risks. Each group involved (e.g., the employer and the employees) might see that it has something to gain—or lose—as a result of the study.

Employer ownership of employee records and the absence of a human subjects protection system in settings traditionally remote in philosophy and mission from the typical research setting can increase the risks for subjects and make studies more difficult to manage and oversee. For example, workplaces are not likely to have IRBs onsite or other institutional officers charged with research oversight.

It is important to recognize that even though occupational research can improve the health environment for employees, workers might have legitimate concerns about participating in a study. For example, they might not believe that the study results will actually lead to better protection of their health (versus, for example, a resultant lowering of standards), or they might not feel that they are really free to refuse to participate. They could have concerns about whether the data collected about them will be provided to management or used to exclude them from some benefits, change their work assignments, defer their promotions, or eliminate their jobs. Management and unions might fear that the study results will be interpreted to justify or undermine a management decision, influence contract negotiations, affect workers' compensation, or alter an employer's liability.

These diverse personal, legal, and economic concerns create unique challenges for the ethical conduct of occupational research. This chapter identifies some of the ethical concerns common to studies that involve the worker community and suggests ways to approach and resolve these concerns.¹

B. What Is a Worker Study?

Studies that involve the worker community are typically conducted for one of two purposes:

- 1) to identify the effects of the work environment on worker health or safety; or
- 2) to test the use of equipment and systems.

In the first instance, epidemiologists, statisticians, medical personnel, occupational safety and health personnel, or health physicists may conduct the research. In the second, human factors engineers or psychologists could be the principal investigators (PIs). Workplace environments that might be the sites of such studies could include such diverse settings as chemical factories, hazardous waste

cleanup sites, military installations, National Aeronautics and Space Administration spacecraft, power plants, hospital laboratories, aircraft cabins, or modern office buildings.

In general, worker studies can be defined as research that involves current and/or former workers as subjects and that is designed to increase understanding of the health effects of occupation exposure to radiation, chemicals, and other potential hazards (DOE 2000).

Much of this research may be epidemiological in its approach and may require access to types of worker records, including medical, occupational, and environmental health data, exposure assessment, or dosimetry data. Other studies may require an individual to submit to specialized testing, physicals, screening exams, and interviews. Some worker studies may evaluate the effectiveness of existing standards to (1) establish the levels of protection necessary to prevent or minimize illnesses related to occupational or environmental exposures or (2) identify workers at risk of future diseases. The results of these studies can provide a basis for protecting the health of the worker community. They can also pose a significant risk of harm to the physical, emotional, or economic well-being of the worker-subject. In clarifying the meaning of research in the context of occupational settings, it is worth revisiting the attributes of research according to the provisions of the Common Rule.

**worker studies
can protect the
health of the
worker
community**

Attributes of Research

A study is viewed as research when (1) the intent of the project is to gather data and contribute to generalizable knowledge to improve public health practice; (2) the intended benefits of the project may or may not include study subjects but always extend beyond the study participants, usually to society; and (3) the data collected exceed requirements for care of the research subjects.

Generalizable knowledge means new knowledge or information that is added to a body of knowledge. Knowledge that can be generalized is collected under systematic procedures that reduce bias, allowing the knowledge to be applied to populations and settings that are different from the ones from which it was collected. Generalizable, for purposes of defining research, does not refer to the statistical concept of population estima-

**concept of
generalizable
knowledge**

¹ Much of this chapter is based on DOE's *Creating an Ethical Framework for Studies That Involve the Worker Community—Suggested Guidelines* and Rose and Pietri's "Workers as Research Subjects: A Vulnerable Population" (DOE 2000; Rose and Pietri 2002).

tion or to the traditional public health method of collecting information from a sample to understand health in the population from which the sample came.

Attributes of Nonresearch

Some studies of workers might not constitute research in the regulatory sense. The intent of a nonresearch activity is to identify and control a health problem. The intended benefits of the project are primarily or exclusively for the subjects or the subject communities; the data collected are needed to assess and/or improve the health of the subjects or the subjects' communities; and project activities are not experimental.

For example, the monitoring of individual workers as part of an established occupational medical program and the collection of data solely for remedial treatment of workers are

routine health surveillance

not considered research. Occupational health surveillance is the routine monitoring, follow-up, and assessment for apparent departures from typical or expected health status among workers. Routine health surveillance involves the standardized, ongoing collection of limited data pertaining to each worker's occupational exposures, demographic characteristics such as age and sex, and information concerning health events of interest. Data are periodically analyzed by diagnostic categories, occupational groups, and other relevant categories to identify trends or departures from previously observed rates that may indicate an emergent risk to worker health. The intent of occupational health surveillance is to protect the health of workers through risk identification. As such, it is not considered research and does not require IRB review. In some cases, medical surveillance might be required by law to protect the health of the workforce. Thus, it is especially critical that if such data are eventually used for research purposes, the privacy of individuals is protected, as they might not have had the option to not participate in the medical surveillance activities.

If a surveillance project includes multiple components and at least one of these components is designed to produce generalizable knowledge, then the entire project is classified as research—unless the components are separable—for regulatory purposes.

The intended use of collected data may not be changed without revisiting the question "Is it research?" A nonresearch project may produce generalizable knowledge after the project is undertaken, even though generating this knowledge was not part of the original primary intent. In this case, because the primary intent was not to generate or contribute to generalizable knowledge, the project does not possess the attributes of research at the outset. However, if a request

is made to use the data obtained in monitoring or treating individual workers in order to study other or more general groups of workers, then the intended use becomes re-research. At that point, the workers whose data will be analyzed must be considered research subjects.

As a consequence, researchers, employers, and others involved in worker studies must comply with all applicable federal regulations and ensure that risks to employees are addressed. Those who fund, approve, and conduct worker health studies must also fully understand these risks and their own responsibilities for avoiding or reducing them.

C. Workers as a Vulnerable Population

Employees may be a vulnerable group chiefly because they may experience management pressure to participate, not participate, or respond to a study in some way that the employer may perceive as advantageous.

The unique risks to workers who are subjects in occupational and health-related research include the potential impact of study findings on individual entitlements, the potential to impair family relationships, and possible threats to job retention, job advancement, and insurability through real or perceived coercion to participate or because of study results. The findings from worker studies may have significant financial implications for individuals, corporations, and the government; thus, there could be intentional or unintentional pressure placed upon employees to ensure a favored outcome. (For the same reasons, there could be intentional or unintentional pressure by employees or employee unions placed upon employers to ensure a favored outcome.)

impact of study findings on individual entitlements

Workers who feel pressured to consent to a study or who are placed in situations in which their ability to give informed consent is compromised, diminished, or negated or in which the results could affect their livelihood or personal security can thus be classified as vulnerable and in need of special consideration.

In addition to the possibility of coercion, worker-subjects also face risks in the areas of privacy and confidentiality. Access by one or several organizations to both research data about an individual and that person's occupational records—especially health records—increases the chance of breach of confidentiality. The possibility that research data about the worker could become part of a record that is provided to insurance carriers, the employer, or future employers is a specific risk for worker research subjects.

Creating an ethical framework that addresses these special risks of worker studies requires a considered and balanced approach, and researchers must follow rules in order to protect and inform anyone who participates as a research subject.

D. Genetic Information in Worker Studies

Genetic information gathered intentionally or unintentionally through worker studies presents unique challenges because it may reveal genetic information about a potential disease or other trait not yet expressed that could have significantly harmful consequences on the subject's future employability, insurability, and/or socioeconomic status.

potential for loss of health care and life insurance or discrimination in employment

(Chapter 24 of this resource manual addresses the special protections required in some types of genetic studies, which apply equally to studies in which the subjects are workers.)

An individual's genetic information may be of interest to a wide variety of individuals and organizations. Insurers and employers may want to use it as a predictor of future illness, to determine future health-care costs, or to determine the ability to perform a job. Family members, educational institutions, or the courts may also want access to genetic information. There have been cases where genetic information has been used to deny medical benefits to retirees who have illnesses with a known genetic basis. Cases of insurance and employment discrimination based on genetic information also have been reported.

Within the worker community, concerns about the potential for loss of health care and life insurance or discrimination in employment are real. The problem is further compounded by the fact that genetic samples are, by their very nature, identifiers. The combination of these forces, and the possible economic consequences to the worker-subject, makes workers a vulnerable population with respect to genetic or other medical information, samples, or data when collected as part of a worker health survey or worker study.

Genetic testing or screening should never be mandatory, especially in the workplace. Ideally, when genetic screening or testing is to be conducted as part of a research study, professional genetic counseling is essential if the test results may entail choices or economic consequences for the person tested and his/her family.

Distinct from genetic testing and screening is genetic monitoring, which involves the periodic examination of employees to evaluate acquired modifications to their genetic material, such as chromosomal damage or evidence

of increased occurrence of mutations that might have developed in the course of employment from exposure to toxic substances. The intent of such monitoring is typically to respond to the effects of such exposure or to control the adverse environmental exposures in the workplace. Such monitoring could be a component of occupational health surveillance and as such is not generally considered to be research, unless the results are then generalized to other populations. The intent of monitoring should be to protect worker health.

Regardless of the initial intent of the collection of genetic data, researchers and all stakeholders must understand that the improper use of genetic screening data in the workplace can expose individuals to risks that affect their employability, insurability, livelihood, and family relationships. Researchers also must be aware that tissue samples collected and stored for nongenetic purposes will contain genetic information and must be protected from potential misuse in the same manner as stored medical data or records of genetic test results (see also Chapter 18).

E. Considerations for IRB Review

Once it has been determined that the proposed investigation does constitute research that is subject to the Common Rule, individuals who participate in worker studies are protected by the Common Rule, which requires that all research involving human subjects that is supported, conducted, or regulated by federal agencies that are signatories to the Common Rule must be reviewed by an IRB. Many additional effective safeguards to protect the confidentiality of research subjects are available. The Federal Privacy Act of 1974, for example, protects health, research, and other records held by federal agencies. Additionally, an executive order restricts the use of genetic information by federal agencies in determining the health insurance eligibility of workers or employment decisions. Currently, several state and federal laws restrict some access to genetic information by health insurance carriers and employers (see Chapter 13).

Federal Privacy Act of 1974

Whenever possible or feasible, local or onsite IRBs overseeing workplace studies should have a worker member or consultant and should review all proposed and continuing studies. When the researcher is not employed by an organization at the study site, the local IRB review may be coordinated with an IRB at the researcher's home institution or, if no other recourse is available, to serve as the sole IRB of record. Because of the nature of occupational sites, the nonbiomedical nature of occupational studies, and the fact that most occupational sites are not philosophically attuned to research, creative solutions may need to be found for IRB

review at an assured institution (see Chapter 5). However, the IRB that conducts the review should be aware of the unique ethical issues affecting the worker community.

Although the seriousness of these concerns suggests the need for new approaches, safeguards, and scientific and ethical reviews specific to worker studies, currently there is no formal ethical framework that addresses the unique vulnerability of participating workers. In the absence of an established and functional ethical framework for review and of knowledge of or adherence to the Common Rule—and possibly insufficient organizational infrastructure—and despite the good intentions of the researcher, the employer, and other stakeholders, worker-subjects may be denied adequate protection of their autonomy, economic status, and/or social position. Review of occupational studies by a well-constituted IRB that includes a worker consultant or preferably a worker member safeguards against these risks.

The IRB's role includes continued involvement in new issues as they arise during the study. Ideally, the research plan should recognize and involve all stakeholders from the outset. A complete research plan should assure accurate and full communication, appropriate scientific peer review and IRB review, and the dedication of resources to ethical issues and to the conduct of the study.

F. Criteria for the Informed Consent Process and Documentation

To assure respect for persons, the Common Rule requires that each research subject give voluntary, informed consent to his/her participation in a study. For consent to be informed, subjects must have adequate and understandable descriptions of the study purpose and of what is expected of them, and they must be informed of any benefits and/or risks that they may experience. For consent to be voluntary, subjects must not face coercion regarding enrollment, reprisal for their decisions, or loss of benefits from their study results.

A well-designed process for obtaining informed consent will, at a minimum, meet the criteria established by the following questions:

- Has the researcher provided a comprehensive description of the research in lay terms?
- Has the worker had time to consider the proposal?
- Has a knowledgeable person—able to assure worker understanding—explained the details of the worker's participation and the study procedures?
- Have foreseeable risks or discomforts been presented in a realistic, open way that encourages questions from the worker?
- Have the possibilities of unforeseen risks been

explained?

- Does the worker understand how the research methods will protect subjects from any physical, social, or economic risks arising from the study?
- Have the potential benefits of the study to the subject and/or the public been explained?
- Where applicable, have alternative courses of treatment been explained to the worker?
- Has compensation for cost to subjects been addressed?
- Is a feedback system in place to keep workers informed of progress and results?
- Has the worker's preference for the right to know or not know individual study results been determined?
- Has the worker been assured that best efforts will be made to maintain confidentiality (to the extent to which confidentiality can be protected) and privacy (up to the defined limits)?
- Does the worker understand the use of preexisting data or previously collected tissue samples and any foreseeable potential future use of data and/or tissues?
- Has the worker been assured that participation is voluntary and that he/she has the freedom to withdraw at any time without penalty or loss of benefits to which he/she is entitled?
- Does the worker understand what recourse he/she has should participation be coerced?
- Have the project manager, PI, IRB contact, and counselor been identified and their functions described?
- Has a copy of the consent form been provided to the worker?
- Has the worker been given the name and telephone number of someone to contact with questions or concerns?

G. Expectations of Privacy and Confidentiality

Protection of subjects' privacy—and the confidentiality of information about subjects—are essential for the successful conduct of worker studies. How the research team handles confidential information about workers will determine whether a relationship of trust will be established and maintained. A worker should have a reasonable expectation that personal information will be disclosed to others only with the worker's permission or in ways that are consistent with the worker's understanding of the original disclosure and the informed consent documents or in ways that are in compliance with the law.

**relationship
of trust**

Various state and federal laws, as well as the require-

ments of IRBs, seek to protect confidentiality of individually identifiable research information. Regardless of the good intention of others for the protection of their privacy, the absolute protection of data cannot be guaranteed. Although penalties exist in both federal and state law for a breach of confidentiality, breaches of confidentiality may be inadvertent, deliberate, or compelled by regulation or law.

The proper management of study data, including clearly defined and strictly followed procedures to protect the confidentiality of study participants, can significantly reduce the possibility of such breaches and must be part of every study design.

Workers' concerns about access to collected research data may cause them to choose not to participate in a study. A related concern about the confidentiality of occupational medical records may lead some workers to choose not to use their workplace health services. For example, a worker might decide not to take part in medical screening, fearing that the results could become known and limit his/her employment, economic advancement, or insurability.

Although participants in a worker study should be aware that future researchers, federal agencies, insurance companies, employers, and others might obtain legal access to the data, it is also true that researchers can protect the confidentiality of data gathered about a subject. Proper management of study data must consider the:

- use of data by others,
- sharing of data,
- use of personal identifiers,
- use of pre-existing data,
- appropriate dissemination of data and results, and
- worker's rights regarding personal data and results.

The data management plan must be a part of the research plan that is approved by the IRB and should also be disclosed when obtaining consent.

The IRB, researchers, and potential subjects must be informed of the limits and loopholes in the privacy laws governing workplace medical and research records, as well as ownership of the data (that may or may not be the property of the employee) and applicable state and local laws.

H. Other Stakeholder Interests

Although the interests of worker-subjects are paramount in occupational research, all stakeholders must be aware of and participate in addressing the special needs and issues that apply. The number of worker-related studies has increased significantly in recent years because of employee health and safety fears and/or political concerns about exposures and risks to health. In addition to the workers and the researchers, many other stakeholders have concerns

and responsibilities that should be considered in a worker study.

Employers are often concerned—if not threatened—by the possible cost and economic impact to their business resulting from the publication or dissemination of worker health study results. However, most employers recognize that early detection of identifiable health problems typically results in lower costs over longer periods. The employer's attitude and cooperation are important in achieving broad worker acceptance of and participation in a health study and successful study outcomes.

Responsibilities of employers include:

- assuring that the study process is thoroughly understood by management
- requiring that the study undergo scientific peer review
- participating in the development and design of the study, where appropriate
- assessing the risks and benefits to both employees and employers
- knowing and understanding the rights of subjects
- assuring that the worker community has full knowledge of the research study
- knowing and understanding the conditions of the study
- abiding by the protocol
- following through with all commitments
- maintaining an active role and relationship with researchers
- assuring that workers, unions, and communities are aware of studies

Unions also might take an active role in protecting the interests of workers. Because a union often serves as a major source of information and influence on members, it can be an active stakeholder in any study involving its members, and, in some cases, the union's cooperation could be essential to a study's success. Union goals, however, may not be identical to those of the individual workers. Nonetheless, unions can be instrumental in study planning, ensuring that worker concerns are addressed, communicating information about the study and study results, and encouraging the use of policies and procedures that promote the overall occupational health of the workforce.

The employer, the union, the researcher's home institution, the IRB, the funding agency, the local community and larger public, and the government at appropriate levels must actively work in partnership to follow the applicable guidelines and to attempt to reconcile potentially conflicting expectations or activities. All stakeholders' roles should be considered when balancing the risks and benefits of research.

Key Concepts: Workers as Research Subjects

- When workers are the subjects of research, the design of the study must assure that subjects' rights and welfare are protected.
- Projects with workers as subjects are considered research when their intent is to produce generalizable knowledge—that is, they are to be used for purposes beyond health monitoring and the care of the individual employees.
- The unique vulnerabilities of worker-subjects include the threat or possibility of coercion; potential effects on job retention, job advancement, and insurability; and possible loss of personal and family privacy.
- The intent of occupational health surveillance is to protect the health of workers through risk identification. As such, it is not considered research and does not require IRB review. However, if a request is made to use the data obtained in monitoring or treating individual workers in order to study other or more general groups of workers, then the intended use becomes research. At that point, the workers whose data will be analyzed must be considered research subjects.
- Protecting the privacy of worker-subjects and the confidentiality of any information acquired about them during the course of research is particularly important in worker studies because of the possible personal or economic damage to the worker that could result from the release of confidential data.
- Genetic testing or screening should never be mandatory, especially in the workplace.
- Wherever possible or feasible, local or onsite IRBs overseeing workplace studies should have a worker member or consultant and should review all proposed and continuing studies.

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Chapter 21

Vulnerable Subjects

- A. Introduction
- B. Elements to Consider in Reviewing Research with Potentially Vulnerable Populations
- C. Additional Department of Health and Human Services Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research—Subpart B
- D. Additional Department of Health and Human Services Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects—Subpart C
- E. Additional Department of Health and Human Services Protections for Children Involved as Subjects in Research—Subpart D
- F. Other Potentially Vulnerable Populations

Key Concepts

References



A. Introduction

The obligation to provide special additional protections for vulnerable subjects derives directly from the ethical principles articulated in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (Belmont Report)* (National Commission 1979). The principle of respect for persons incorporates at least the following two ethical convictions: individuals should be treated as autonomous agents and persons with diminished capacity for autonomy are entitled to extra protections. When diminished autonomy compromises a person's ability to exercise free and informed choice, that person becomes vulnerable to coercion or undue influence and is entitled to special protections.

The ethical principle of beneficence as applied to research involving vulnerable subjects asserts that judgments regarding the nature, probability, and magnitude of potential harm versus the potential benefits of the research are altered when vulnerable subjects will be involved. Special protections are needed to ensure that anticipated benefits to the subjects genuinely outweigh reasonably foreseeable risks.

The ethical principle of justice requires the equitable selection of subjects. Yet, in the words of the *Belmont Report*, socially, educationally, or economically disadvantaged persons, sick persons, and persons who are institutionalized

may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition (National Commission 1979, 8).

In general, individuals can be considered to be vulnerable to coercion or undue influence in the research setting either because they have difficulty providing voluntary, informed consent (as in the case of children), because of situational circumstances (as in the case of prisoners or the homeless), or because they are at higher risk for exploitation (as in the case of the terminally ill). By properly protecting those who

vulnerable to coercion or undue influence

are sometimes or always vulnerable, justice can be served by allowing these individuals or groups to participate in and possibly benefit from the outcomes of research.

Many groups have struggled with defining the concept of vulnerability, trying to add clarity. For example, the National Bioethics Advisory Commission (NBAC) recommended that vulnerability should be characterized in terms of situations that may create susceptibility to harm or coercion rather than in terms of specific categories of persons. Instead of excluding groups of subjects because they may be vulnerable, NBAC recommended designing studies that reduce the risks of exploitation (NBAC 2001).

B. Elements to Consider in Reviewing Research with Potentially Vulnerable Populations

IRBs that regularly review research involving vulnerable subjects should include members who are knowledgeable about and experienced in working with the type of vulnerable subjects involved in such research (§____.107(a); 21 CFR 56.107(a)).

Regulations require that when some or all of the subjects of a proposed research protocol are likely to be vulnerable to coercion or undue influence, IRBs, in order to approve the research, must ensure that additional safeguards have been included to protect the rights and welfare of such subjects (§____.111(b); 21 CFR 56.111(b)). Examples of vulnerable subjects listed in the regulations include children, prisoners, pregnant women, mentally disabled persons, and economically or educationally disadvantaged persons.

The Department of Veterans Affairs (VA) considers veterans to be potentially vulnerable to coercion because the VA may be their only source of medical care, and they may view participation in research as an obligation to fulfill in return for care received or as a patriotic service.

Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) regulations require specific protections for children. DHHS regulations also require specific protections for prisoners, pregnant women, human fetuses, and neonates. If an institution's assurance (see Chapter 5) is on file with OHRP and applies to all research regardless of source of funding, then the specific protections for these populations would have to be extended to all research studies.

In fulfilling their obligation to ensure special protections for vulnerable subjects, Institutional Review Boards (IRBs) must pay special attention to specific elements of the research plan in order to identify situations that may make subjects particularly vulnerable to coercion or undue influence. To do so, IRBs must consider both individual and group characteristics, including the economic, social, physical, and environmental conditions of potential subjects. Protocol elements to examine closely include:

- inclusion and exclusion criteria for selecting and recruiting participants;
- procedures for obtaining informed consent and ensuring voluntary participation; and
- possible sources of coercion and undue influence.

Investigators generally should not be permitted to overselect or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.

When necessary, an IRB should obtain information regarding the laws and science that bear on the decisionmaking capacity of the

potentially vulnerable populations that may be involved in the research reviewed by the IRB. Research studies that involve potentially vulnerable populations should have

assessing subjects' capacities, comprehension, and abilities

adequate procedures in place for assessing subjects' capacities, comprehension, and abilities to provide voluntary informed consent or assent. When weighing the decision to approve or disapprove research involving vulnerable subjects, an IRB must determine whether such procedures are included in the research plan.

When warranted, the IRB may require researchers to implement procedures for ensuring adequate understanding of information presented to prospective subjects who are likely to be vulnerable to coercion or undue influence. For example, IRBs may require provisions for using independent consent monitors or a subject advocate, reading the consent document to subjects slowly to gauge their understanding paragraph by paragraph, encouraging subjects to ask questions, and translating informed consent documents into languages that subjects can understand.

Subjects must always receive an informed consent document written in a language understandable to them, unless the IRB formally waives the requirements for informed consent or for written documentation of informed consent. Providing subjects who do not understand English with an informed consent document written in English is not

permissible, even if a translator is available during the informed consent conference. Other protections that the IRB may require include:

- testing subjects' understanding before enrollment;
- submitting each signed informed consent document to the IRB; and
- establishing a waiting period between initial contact and enrollment to allow time for family discussion and questions.

(See Chapter 12 for a more extensive discussion of the informed consent process.)

If a person becomes vulnerable during the course of research, it is the duty of the investigator to institute additional protections or possibly remove that individual from the study.

C. Additional DHHS Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research— Subpart B

DHHS regulations at 45 CFR 46, Subpart B, detail special additional protections for research involving pregnant women, human fetuses, and neonates (newborns). Under these regulations, IRBs are required to document specific findings to minimize the risk of harm or discomfort to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk. On the other hand, an IRB should not, in order to avoid risk, permit the unilateral exclusion from research of women who are not pregnant but who could become pregnant. Exclusion requires compelling scientific justification (CDC 1996; FDA 1993; NIH 2001). Where such justification exists, the IRB may be alerted to the possibility that it is also scientifically warranted to exclude men of reproductive potential.

The basic definitions used in 45 CFR Part 46 Subpart B appear in Table 21.1.

Six categories, each with its own requirements for IRB determinations, apply to research with pregnant women, human fetuses, and neonates under Subpart B. The regulations require that an IRB perform a systematic analysis of the risks, benefits, and informed consent procedures for each specific category of prospective subjects. IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category should be clearly documented in an IRB's records. Table 21.2 summarizes these categories and considerations regarding IRB approval.

Table 21.1
Summary of Basic Definitions in DHHS 45 CFR 46 Subpart B (45 CFR 46.202)

Term	Definition
Pregnancy	The period of time from implantation until delivery.
Delivery	Complete separation of the fetus from the woman by expulsion or extraction or any other means.
Fetus	The product of conception from implantation until delivery.
Dead fetus	A fetus that exhibits neither a heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
Nonviable fetus	A neonate after delivery that although living is not viable.
Viable fetus	A fetus that is able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.
Neonate	A newborn.

Research Involving Pregnant Women or Fetuses.

Under Subpart B (45 CFR 46.204), pregnant women or fetuses may be involved in research only if all of the following conditions are met:

- Scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and have provided data for assessing potential risks to pregnant women and fetuses.
- The risk to the fetus is caused solely by interventions or procedures that hold the prospect of providing direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means.
- Any risk is the least possible risk for achieving the objectives of the research.
- If the research holds the prospect of providing direct benefit to the pregnant woman or to both the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the informed consent of the pregnant women is obtained in accordance with the informed consent provisions of Subpart A of 45 CFR Part 46.
- If the research holds out the prospect of direct benefit solely to the fetus, then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of Subpart A of 45 CFR Part 46, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- Each individual providing consent under the preceding two paragraphs above is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
- For children (45 CFR 46.402(a)) who are pregnant, assent of the pregnant child and permission of the pregnant child's parent(s) are obtained in accord with the provisions of Subpart D of 45 CFR Part 46.
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- Individuals engaged in the research will have no part in any decisions regarding the timing, method, or procedures used to terminate a pregnancy.
- Individuals engaged in the research will have no part in determining the viability of a neonate.

Research Involving Neonates: Basic Requirements.

Neonates may be involved in research only if all of the following conditions are met (45 CFR 46.205(a)):

- Where scientifically appropriate, preclinical and clinical studies have been conducted and have provided data for assessing potential risks to neonates.
- The individuals providing consent as noted below are fully informed regarding the reasonably foreseeable impact of the research on the neonate.
- Individuals engaged in the research will have no part in determining the viability of a fetus.

Research Involving Neonates: Neonates of Uncertain Viability. Until it has been determined that a neonate is viable, a neonate may not be involved in research unless the following *additional conditions* are met (45 CFR 46.205(b)):

- The IRB determines that (1) the research holds out the prospect of enhancing the probability of survival of the particular neonate to the point of viability, and any risk is the least possible for achieving the objectives of the research or (2) the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means, and there will be no added risk to the neonate resulting from the research.
- The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR (legally authorized representative) is obtained in accordance with Subpart A of 45 CFR Part 46, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Research Involving Neonates: Nonviable Neonates.

Under Subpart B, a nonviable neonate is a neonate after delivery that although living is not viable (45 CFR 46.202(e)). After delivery, a nonviable neonate may not be involved in research unless *all of the following additional conditions* are met (45 CFR 46.205(c)):

- Vital functions of the neonate will not be artificially maintained.
- The research will not terminate the heartbeat or respiration of the neonate.
- There will be no added risk to the neonate resulting from the research.
- The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.
- The legally effective informed consent of both parents of the neonate is obtained as required under Subpart A

of 45 CFR Part 46, except that the waiver and alteration provisions of 45 CFR 46.116(c) and 46.116(d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice.

Research Involving Neonates: Viable Neonates. A neonate that has been determined after delivery to be viable is a child as defined under Subpart D (45 CFR 46.402(a)) and may be included in research only to the extent permitted under Subparts A and D (45 CFR 46.205(d)).

Research Involving the Placenta, Dead Fetus, or Fetal Material After Delivery. Under Subpart B, a dead fetus is a fetus after delivery that exhibits neither heartbeat, spontane-

ous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (45 CFR 46.202(a)).

After delivery, research involving the placenta, the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities (45 CFR 46.206) (see also Chapter 26 of this guide).

It is important to note that if information associated with the material described above is recorded for research purposes in such a way that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects, and all pertinent requirements of 45 CFR 46 must be met.

Table 21.2

Summary of Subpart B Categories and Approval Considerations

Category	45 CFR §	Criteria
Pregnant women or fetuses	46.204	Preclinical studies, direct benefit or minimal risk, consent authority of mother/father, full consent information, assent of pregnant child, no influence on pregnancy termination, no influence on viability determination
Neonates (basic criteria)	46.205(a)	Preclinical studies, full assent information, no influence on viability determination
Neonates: Uncertain viability	46.205(b)	Enhance probability of survival or no added risk, consent of the Legally Authorized Representative (LAR) of either or both parents
Neonates: Nonviable	46.205(c)	No artificial maintenance of vital functions, no termination of heartbeat or respiration, no added risk, informed consent of both parents if available, no use of legally authorized representatives
Neonates: Viable	46.205(d)	Subpart D (children) applies
Placenta, dead fetus, fetal material after delivery	46.206	Applicable federal, state, local laws and regulations
Not otherwise approvable	46.207	IRB recommendation, expert Secretarial panel recommendations, Secretarial determination

Research Not Otherwise Approvable Under

Subpart B—Special Review. Research involving pregnant women, human fetuses, or neonates that is not otherwise approvable under Subpart B may be approved after special review by DHHS (45 CFR 46.207). DHHS will conduct or fund research that the IRB does not believe meets the requirements of 45 CFR 46.204 or 45 CFR 46.205 only if:

- the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates; and
- the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law) and following an opportunity for public review and comment (including a public meeting announced in the *Federal Register*), has determined either
 - 1) that the research in fact satisfies the conditions of 45 CFR 46.204 or
 - 2) the following:
 - i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates;
 - ii) the research will be conducted in accordance with sound ethical principles; and
 - iii) informed consent will be obtained in accordance with the informed consent provisions of Subpart A of 45 CFR Part 46 and applicable sections of Subparts B, C, and D of 45 CFR Part 46.

As of the date of this publication, DHHS has not approved any research involving pregnant women, human fetuses, or neonates that required consultation with experts and public comment. It is assumed that the consultation process would be similar to that used for review of research involving children (see below), with the addition of a public meeting.

D. Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects — Subpart C

DHHS regulations at 45 CFR 46, Subpart C, detail special additional protections for research involving prisoners who, because of their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research.

A prisoner is defined as any individual *involuntarily confined or detained* in a penal institution (45 CFR 46.302(c)). This includes the following:

- persons who are sentenced under a criminal or civil statute
- persons detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution
- persons detained pending arraignment, trial, or sentencing

Thus, the defining characteristic for a prisoner under the regulations is being “detained” in a “penal” facility, or being “detained” in another “facility as an alternative to prosecution or incarceration.” Persons who are not “detained” are not prisoners, even if they are participating in a program in lieu of prosecution or incarceration.

To review research involving prisoners covered by the DHHS regulations, IRBs must:

- have a majority of its members not otherwise associated with the prison (45 CFR 46.304(a)); and
- include a prisoner or a prisoner representative with appropriate background and experience to serve in this capacity, unless the research has already been reviewed by an IRB that included a prisoner or prisoner representative (45 CFR 46.304(b)).

To approve research involving prisoners, the IRB must:

- make all determinations required under the DHHS regulation at 45 CFR 46.305(a), including determining that the research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2).

If the research is DHHS conducted or supported, the institution engaged in the research must certify to the Office for Human Research Protections (OHRP) that the duties of the IRB under 45 CFR 46.305(a) have been fulfilled. Certification to OHRP is not required for research that is not supported by DHHS. However, OHRP recommends that the IRB apply the standards of Subpart C to all prisoner research. Should non-DHHS research fall outside the category stipulations under 45 CFR 46.306, OHRP recommends that the IRB consult with appropriate experts before approving the research.

Following receipt of the research proposal, OHRP will determine which, if any, of the four categories of research permissible under DHHS regulations at 45 CFR 306(a)(2) that the proposed research meets. OHRP will consult with appropriate experts with respect to certain research that falls under paragraphs (iii) and (iv) of 45 CFR 46.306(a)(2). When

applicable, OHRP also will publish in the *Federal Register* a notice of intent to approve such research. DHHS-conducted or DHHS-supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to the institution on behalf of the secretary under 45 CFR 46.306(a)(2).

Under DHHS regulations, prisoners may participate in the following categories of research:

- studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior;
- studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons;
- research on particular conditions affecting prisoners as a class (providing the secretary of DHHS has consulted with appropriate experts and published the intent to support such research in the *Federal Register*);
- research involving practices (e.g., clinical research studies) that have the intent and reasonable probability of benefiting the prisoner subject. If the research involves possible assignment to a control group that may not benefit from the research, the secretary of DHHS must also consult with appropriate experts and publish the intent to support the research in the *Federal Register* (45 CFR 46.306).

The following additional determinations must be made by the IRB before research involving prisoners goes forward (45 CFR 46.305):

- The research under review is limited to one of the categories of research listed above.
- Any possible advantages accruing to the prisoner through his/her participation in the research—such as improvement in general living conditions, medical care, quality of food, amenities, and opportunities for earnings—are not of such a magnitude that his/her ability to weigh the risks of the research against the value of such advantages in the prison environment (which is one of limited choices) is impaired.
- The risks involved in the research are commensurate with the risks that would be accepted by nonprisoner volunteers.
- Procedures for selecting subjects within the prison are fair to all prisoners and are immune from arbitrary intervention by prison authorities or other prisoners. Unless the Principal Investigator (PI) provides the IRB with justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners that meets the characteristics needed for a particular research project.

- Information about the research presented to prisoners is in language that is understandable to the subject population.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research when making decisions regarding parole and that each prisoner is clearly informed in advance that participation in the research will have no effect on his/her parole.
- When the IRB determines that follow-up examination or care of participants may be needed after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of prisoners' sentences, and for informing participants of this fact.

The requirement for follow-up after participation when appropriate, is often overlooked by IRBs that are reviewing research involving prisoners. IRBs must carefully evaluate whether follow-up examination or care is needed and, if so, determine if the necessary actions will be taken to ensure contact after the subject leaves the prison.

Research Not Otherwise Approvable Under Subpart C—Special Review. As indicated above, DHHS-supported prisoner research involving a condition affecting prisoners as a class or assignment to control groups that might not benefit from the research may only proceed after the Secretary of DHHS “has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice in the *Federal Register*” of the intent to approve the research (45 CFR 46.306(a)(2)). OHRP performs this consultation and publishes the required *Federal Register* notice on behalf of the Secretary. Typically, OHRP selects a group of experts who meet to review the proposed research. Each expert submits a separate written recommendation on whether the research should be conducted. The recommendations generally include a risk-benefit analysis similar to that conducted by IRB members and a discussion of ethical issues relating to the research.

Acting on behalf of the Secretary of DHHS, OHRP (not the expert group) makes the final determination about whether the research may go forward, obtains the necessary DHHS administrative clearances, and publishes the *Federal Register* notice. Approval of the research is by no means automatic, and several proposed studies have been rejected outright or modified substantially before they were allowed to proceed. Any study that involves prisoners simply as a matter of convenience is certain to be rejected.

On May 19, 2003, OHRP posted “OHRP Guidance on the Involvement of Prisoners in Research.”¹ The new document replaces the prisoner research guidance document titled

¹ See www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm.

“OPRR Guidance on Approving Research Involving Prisoners” (May 19, 2000). The new guidance also provides additional clarification on the responsibilities required of IRBs and institutions under Subpart C.

The new guidance includes the following two significant changes that will require alterations to the Standard Operating Procedures of IRBs and institutions:

1. Under Section F., “Permitted Research Involving Prisoners,” the guidance states that “the institution engaged in the research must certify to the Secretary (through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305.” Previously, the guidance directed the IRB to provide this certification. In the same section, OHRP has deleted the statement, “Where an institution holding an OPRR-approved Multiple Project Assurance (MPA) wishes to involve prisoners in non-HHS-supported research, certification is not required.”
2. OHRP has revised Section H, “Responsibilities of Institutions,” to require the institution “responsible for the conduct of the proposed research” to submit a copy of the research proposal so that OHRP can “determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2)...” and further states that the “term ‘research proposal’ includes the IRB-approved protocol, any relevant HHS grant application or proposal, any IRB application forms required by the IRB, and any other information requested or required by the IRB to be considered during initial IRB review.”

IRBs will have to reexamine their current procedures for reviewing and documenting the review of research involving prisoners to incorporate procedures for notifying the institutional official when they receive such a research proposal. The procedures should include methods for reminding investigators that all research interactions and interventions with subjects who become prisoners must cease until all of the requirements of Subpart C have been satisfied.

Because OHRP has stated in the new guidance that under “special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.” The IRB will have to institute procedures to document the PI’s assertion and the chairperson’s agreement or disagreement with that assertion.

Investigators should ensure that they understand their responsibility to notify the IRB and the sponsor, if applicable, if a subject enrolled in a study becomes a prisoner. Investigators should have a method to document and substantiate that it would be in the subject’s best interest to continue in the study.

On June 20, 2003, the Secretary of DHHS issued a final notice that it has waived the applicability of certain provisions of Subpart C (Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects.

This waiver will allow DHHS to conduct or support certain important and necessary epidemiological research that would not otherwise be permitted under Subpart C. The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain epidemiological research conducted or supported by DHHS:

- in which the sole purposes are:
 - to describe the prevalence or incidence of a disease by identifying all cases, or
 - to study potential risk factor associations for a disease, and
- where the institution responsible for the conduct of the research certifies to OHRP that: the institutional review board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and determined and documented that
 - the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
 - prisoners are not a particular focus of the research.²

E. Additional DHHS Protections for Children Involved as Subjects in Research—Subpart D

DHHS regulations at 45 CFR part 46, Subpart D, and FDA regulations at 21 CFR Part 50, Subpart D, require that special protections be provided for research involving children. Under the regulations, children are defined as persons who have not attained the “legal age” (in their jurisdiction) for consent to treatments or procedures that may be involved in the research, under applicable law of the jurisdiction in which the research will be conducted.

² See www.hhs.gov/ohrp/references/fr06-20.pdf.

When reviewing research involving children, IRBs must make certain specific findings and determinations. In particular, IRBs must ensure that:

- a risk-benefit analysis has been conducted;
- the research falls into one of the permitted regulatory categories;
- adequate provisions have been made to solicit parental permission; and
- adequate provisions have been made to solicit the assent of the child.

Risk-Benefit Analysis. The records of an IRB should reflect its understanding of and justification for the risks and benefits posed by approving research that involves children.

Permitted Categories. Based in part on its risk-benefit analysis, in order for the research to be approved, the IRB must find and document that the proposed research falls within one of the following four categories:

1. Research that does not involve greater than minimal risk
2. Research involving greater than minimal risk, but presenting the prospect of providing direct benefit to the individual subjects
3. Research involving greater than minimal risk and with no prospect of providing direct benefit to individual subjects, but that is likely to yield generalizable knowledge about the subject's disorder or condition
4. Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

Each category stipulates specific conditions that must be met before the proposed research can be approved. These conditions are summarized in Table 21.3. The IRB should document its determination about the appropriate category and provide protocol-specific justification demonstrating that the pertinent criteria have been satisfied (see OHRP's *Compliance Activities: Common Findings and Guidance*).³

Parental Permission. The IRB must determine that adequate provisions are made for obtaining and documenting parental permission for a child's participation in research. Depending on the category in which the research falls (see Table 21.3), the permission of one or both parents may be required as a condition of a child's participation.

DHHS regulations at 45 CFR 46.408(c) permit the IRB to waive the requirement for parental permission in minimal risk research, to the same extent that it is permitted to waive

the informed consent requirement for research involving adults under 45 CFR 46.116(d) of the Common Rule. In other words, the IRB may waive the requirement for parental permission when it finds and documents that:

- the research involves no more than minimal risk to subjects;
- the waiver would not adversely affect subjects' rights and welfare;
- the research could not practicably be carried out without the waiver; and
- where appropriate, additional information will be provided after participation.

The same section of the DHHS regulations further permits the IRB to waive or alter the requirement for parental permission where "parental permission is not a reasonable requirement to protect the subjects (e.g., neglected or abused children)."

FDA regulations do not include either of these waiver provisions (i.e., for minimal risk research or where permission would not protect the children).

Assent of the Child. The IRB must also determine that adequate provisions are made for soliciting the assent of children, when in the judgment of the IRB they are capable of providing assent. In determining whether children are capable of assenting, the IRB must take into account their ages, maturity levels, and psychological state. This judgment may be made for all children to be involved in research under a particular protocol, or for each individual child, as the IRB deems appropriate.

Investigators should not necessarily treat children as rational, autonomous decisionmakers, but they should give serious consideration to each child's developing capacity for participating in decisionmaking, including rationality and autonomy. Assent should include at least the following elements:

- helping the child achieve a developmentally appropriate awareness of the nature of his/her condition as it relates to the research
- telling the child what he/she can expect with tests and treatment(s)
- making an assessment of the child's understanding of the situation and the factors influencing how he/she is responding (including whether there is inappropriate pressure to accept testing or therapy)
- soliciting an expression of the child's willingness to participate in the research⁴

³ See www.hhs.gov/ohrp/references/findings.pdf.

⁴ See www.aap.org/policy/00662.html.

When Assent Is Not Required. The assent of the child is not a necessary condition for the research if an IRB determines that:

- the capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- the intervention or procedure involved in the research holds the prospect of providing a direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

Even when an IRB determines that subjects are capable of assenting, the IRB may still waive the assent requirement if:

- the research involves no more than minimal risk;
- the waiver will not adversely affect subjects' rights and welfare;
- the research could not practicably be carried out without the waiver; and
- when appropriate, the subjects will be provided with pertinent information after participation.

Documentation of Assent. If it is deemed appropriate that the child's assent should be solicited, the assent form should be designed for the child's use and his/her level of understanding. For young children, the assent form should be a relatively brief document, with simple, age-appropriate language that is presented in a manner understandable to the child.

Reasonable Expectation of Benefit. IRBs should take great care in approving research that involves a child who is suffering from a life-threatening illness and who would stand little real chance of therapeutic benefit from the proposed research. IRBs also should take great care in allowing parents to overrule the child's active dissent in cases in which experimental therapy has little or no reasonable expectation of benefit for the child.

Overall, the child's dissent should generally carry more influence as the child approaches the age of majority. The active dissent of a child approaching 18 years of age, for example, is typically afforded more weight than the dissent of an 8-year-old.

Table 21.3
Summary of Subpart D Categories and Approval Considerations

Category	45 CFR § 41 CFR §	Criteria Involve
Minimal Risk	46.404 50.51	<ul style="list-style-type: none"> • Assent of child • Permission of one parent
Greater than minimal risk: Prospect of direct benefit	46.405 50.52	<ul style="list-style-type: none"> • Assent of child • Permission of one parent • Anticipated benefit justifies risk • Benefit is as favorable as alternatives
Greater than minimal risk: No direct benefit but likely to yield generalizable knowledge about the subject's disorder or condition		<ul style="list-style-type: none"> • Assent of child • Permission of both parents • Minor increase over minimal risk • Generalizable knowledge about subject's disorder or condition • Procedures/experiences commensurate with child's actual situation
Not otherwise approvable but presenting an opportunity to understand, prevent, or alleviate a serious problem affecting children	46.407 50.54	<ul style="list-style-type: none"> • IRB recommendation • Expert panel review • Public review and comment • Determination by DHHS secretary or FDA's commissioner of food and drugs

Research Not Otherwise Approvable Under

Subpart D—Special Review. As indicated in Table 21.3, FDA-regulated or DHHS-supported research that poses greater than minimal risk to children and is unlikely to yield direct benefit or generalizable knowledge about the subject’s disorder or condition requires approval by the FDA Commissioner or the Secretary of DHHS following review by a panel of experts and public review and comment.

The consultation process (sometimes called the “407 review” after its description at 45 CFR 46.407) is similar to that used for prisoner research, with the addition of a requirement for public review and comment.

**consultation
processor**

Depending on whether the research is FDA regulated or DHHS supported, FDA or OHRP (or both in collaboration) appoints a panel of experts in appropriate disciplines. The members meet to consider the proposed research, and each expert submits a separate written recommendation on whether the research should be conducted. The recommendations generally include a risk-benefit analysis similar to that conducted by IRB members and a discussion of ethical issues relating to the research.

FDA or OHRP then publishes a notice in the *Federal Register* describing the research and requesting public comments. Information about the research, including the experts’ recommendations described above, is posted on a Web site, and comments are received and considered.

After the announced comment period has ended, FDA or OHRP (depending on whether the research is FDA regulated or DHHS supported) makes the final determination about whether the research may go forward, obtains the necessary administrative clearances, and publishes a *Federal Register* notice describing its determination. As with prisoner research, approval is by no means automatic.

F. Other Potentially Vulnerable Populations

The context of the research is an important consideration for an IRB to consider when reviewing research that involves other potentially vulnerable subjects. As indicated previously, research involving homeless persons, members of minority groups, or the economically or educationally disadvantaged poses significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and the IRB must take such considerations into account.

Some individuals may speak and understand English but be unable to read it. Illiterate persons may have the informed consent read to them and may “make their mark” in

a manner consistent with applicable state law to document their understanding. In this situation, it is also desirable to obtain the signature of a witness to the consent process and the signature of the person conducting the consent interview. Investigators should not enroll subjects who may not truly understand what they have agreed to participate in.

Employees, Former Employees, and Students. Employees, former employees, and students all share the disadvantage of residing at the lower, vulnerable end of a significant power relationship. In each situation, important aspects of the individual’s fate and livelihood depend on remaining on good terms with those who exercise authority over them. Even under the most benign circumstances, coercion or undue influence can occur when employees, former employees, or students are asked to participate in research by those holding authority over them.

Consequently, these individuals should be considered as somewhat vulnerable subjects (although not on the same scale as the groups described above), and an IRB should require special protections to ensure that such groups do not feel either subtle or direct pressure to participate in research.

**somewhat
vulnerable
subjects**

Recent events in which healthy employees or students died as a result of participating in research underscore two important principles to ensure that such individuals are not unduly influenced to become research subjects.

1. An especially careful analysis of the possibility of coercion or undue influence is needed wherever there is no direct benefit to the individual research subject. Unanticipated harms do occur, and their possibility should not be discounted.
2. An especially careful analysis of risks and benefits is also needed even for apparently benign research involving no experimental treatment. The normal risks associated with common clinical procedures (e.g., of lidocaine with bronchoscopy), although routinely considered justifiable in a clinical context, may not be justifiable to the same extent when the only benefit is the advancement of science.

Employees and Former Employees. Individuals invited to participate in research conducted at their work site or by their employer are potentially vulnerable to coercion or undue influence. Most employees cannot afford to jeopardize their jobs by failing to cooperate with research involving the workplace, even though the research may entail considerable risk. Retired employees or other former employees who depend on employer-administered pension or benefit programs are similarly vulnerable.

Employees are obviously vulnerable in the short term, as they may face direct or indirect retaliation by supervisors or others in positions of authority in the workplace should they decline to participate in research endorsed by management. However, many workers may be even more vulnerable in the long term if the research collects identifiable information about their work histories, personal health, or living habits; relationships and family life; or nonwork activities.

Loss of employment, loss or reduction of medical benefits, and damage to coworker relationships are only the most obvious risks for workers who participate in research relating to or occurring in the workplace. IRBs that review research involving workers and former workers should identify all foreseeable risks, require protections against short- and long-term harms, and minimize the possibility of coercion and undue influence.

To guarantee knowledge of the work environment and of the real and perceived risks faced by prospective employee/subjects, IRBs should include one or more employees or former employees in a relevant area of employment as IRB members or consultant reviewers of all proposed research that will enroll employees as subjects. For additional discussion of this topic, see Chapter 20.

Students. It is the tradition in some academic institutions for students who are enrolled in introductory courses to be required to “experience research” as a course requirement and/or for students to receive “extra” course credit for research participation. Where such systems exist, it is extremely important that the IRB enforce specific protections to ensure that students are not coerced into research participation, no matter how innocuous the research might appear to be.

Alternatives to actual participation as a research subject must be provided to all students who are asked to participate in research, and the alternatives must be as convenient and easy to complete as participation in research.

Any system under which students are permitted to serve as research subjects should be governed by formal written procedures approved by an IRB. Under no circumstances should faculty members or others who have authority over students be permitted to involve students in research without specific knowledge of and approval by an IRB.

Economically Disadvantaged Persons. Economically disadvantaged persons may be particularly vulnerable regarding the attractiveness of financial incentives that may accompany participation in research. However, what might seem like modest and reasonable remuneration to a professional person may be unduly inducing a homeless individual, an elderly person on a fixed income, or a student

or other individual who is dependent on an institution for care giving. Even a guaranteed two-week stay on a hospital ward may be unduly attractive to some potential subjects.

IRBs must consider rewards, incentives, and remuneration for research participation. Although it is certainly not fair to underpay subjects because they are poor, it is also unduly inducing to offer incentives that cloud the voluntary nature of their decisionmaking. IRBs must have a thorough understanding of the likely subject population and the conditions of recruitment in order to make a reasoned determination regarding acceptable incentives for research participation.

FDA guidance (*FDA Information Sheets*) emphasizes the following points:

- Payment to research subjects for participation is not considered a benefit; it is a recruitment incentive.
- The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive or presents undue influence.
- Any credit for payment should accrue as the study progresses and should not be contingent on the subject completing the entire study.
- Although the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such incentive is not unduly inducing.
- All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Educationally Disadvantaged Persons. Educationally disadvantaged persons may have difficulty understanding proposed research, or they may feel intimidated by persons whom they perceive as “knowing more” than they do.

IRBs must ensure that the circumstance of enrollment and informed consent address these possible disadvantages. Many of the protections suggested previously, such as simplifying consent documents, encouraging dialogue and questions during the consent conference, requiring waiting periods before final consent is accepted, and involving subject advocates, can be effective in overcoming educational disadvantages.

Mentally Ill or Mentally Disabled Persons. Mentally ill and mentally disabled persons present a particular challenge to IRBs in terms of the ethical principle of respect for persons. On the one hand, persons who are not capable of exercising autonomous judgments deserve protection. On the other hand, persons who are capable of making autonomous decisions must be permitted to do so.

Although protectiveness may be a natural tendency relative to the enrollment of mentally ill or mentally disabled persons in research, persons with mental illness, advocates for the mentally ill, and mental health professionals argue forcefully that mental illness does not necessarily result in a complete inability to make autonomous choices.

The ethical principle of respect for persons requires that IRBs and investigators clearly understand the cognitive and decisionmaking capabilities of prospective subjects who are in some manner mentally ill or mentally disabled. Persons who are capable of exercising informed choice for themselves must not be deprived of the right to do so.

Thus, IRBs must determine the correct balance between freedom to choose and protectiveness. This may entail setting specific standards for assessing the capacity of each prospective subject individually, requiring special efforts to enhance understanding, making efforts to involve significant others as identified by and agreed upon by the prospective subject, and defining precisely when a legally authorized representative is required.

Decisionally Impaired Subjects. Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions.

Other individuals who may be considered decisionally impaired, with limited decisionmaking ability, are those under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps. People facing intensely stressful situations may also suffer temporary decisional impairment.

As indicated at the beginning of this chapter, the IRB should obtain information regarding laws and science that bear on the decisionmaking capacity of those who belong to potentially vulnerable populations related to involvement in the proposed research. Research studies that involve potentially vulnerable populations must have procedures in place for assessing subjects' capacities, understanding, and abilities to provide informed consent or assent. When deciding whether to approve or disapprove research involving vulnerable subjects, the IRB must determine whether any such procedures described in the research plan are adequate for protecting subjects who are likely to be enrolled.

When warranted, the IRB may require researchers to take steps to enhance understanding for potentially vulnerable subjects. Examples include providing a consent monitor or subject advocate and reading the consent document to

subjects slowly to gauge their understanding paragraph by paragraph.

Other protections that the IRB may require include:

- encouraging questions and discussion during the informed consent process;
- testing subjects' understanding before enrollment;
- submitting each signed informed consent document to the IRB; and
- establishing a waiting period between initial contact and enrollment to allow time for family discussion and questions.

Incompetent Subjects and Surrogate Consent. It is absolutely essential for IRBs and research investigators to understand and strictly observe state laws regarding the authority of legally authorized representatives (see Chapter 12) to provide consent for research participation.

Incompetence is a legal concept that involves formal adjudication and appointment of a legal guardian whose authority is clearly stipulated. When the court declares an individual to be incompetent, decisionmaking authority for the individual is ordinarily transferred to another party. Whether, and under whose authority, an incompetent person can be enrolled in research is usually not the issue of concern.

More typical for IRBs and research investigators is the question of what to do about individuals who have not been adjudicated as incompetent but whose capacity to provide legally informed consent is questionable. In these cases, IRBs and investigators must rely on state laws to determine who can act as the prospective subject's LAR for surrogate consent to participate in research.

The major difficulty for IRBs and researchers is that the law in most states is unclear regarding who can serve as a LAR for research participation decisions, as opposed to medical treatment. Although many IRBs and institutions rely on their state's medical treatment statutes to make an inference about the acceptability of LARs for research consent, the law is not settled in most states. Because consensus on this issue has been difficult to achieve in the legislative realm, the question will probably be addressed in state courts before it is addressed by state legislatures.

Consequently, IRBs, institutions, and researchers in most states are at some risk when they choose to accept a LAR's decision for enrollment in research. Although OHRP accepts the written opinion of the institution's legal counsel in this regard, the decision about whether or not to accept a LAR's decision for research enrollment is essentially reduced to a risk-management issue (as opposed to an ethical issue) at many institutions.

Key Concepts: Vulnerable Subjects

- When diminished autonomy compromises a person's ability to exercise free and informed choice, that person is entitled to special protections under the ethical principle of respect for persons.
- When vulnerable subjects are involved in research, special protections are needed under the ethical principle of beneficence to ensure that anticipated benefits genuinely outweigh reasonably foreseeable risks.
- The ethical principle of justice requires that vulnerable subjects be protected from being involved in research solely for administrative convenience or because they are easy to manipulate as a result of their illnesses or socioeconomic conditions.
- Unless an IRB formally waives the requirements for informed consent or for written documentation of informed consent, subjects must always receive an informed consent document written in a language understandable to them.
- To protect vulnerable subjects, IRBs must consider both individual and group characteristics, including the economic, social, physical, and environmental conditions of potential subjects.
- In general, Subpart B of the DHHS human subjects regulations requires that research involving pregnant women and fetuses involve the least possible risk.
- Six categories, each with its own requirements for IRB determinations and protocol-specific documentation, apply to research with pregnant women, human fetuses, and neonates under Subpart B.
- The defining characteristic of a prisoner under Subpart C of the DHHS human subjects regulations is being "detained" in a "penal" facility or being "detained" in another "facility as an alternative to prosecution or incarceration."
- To approve research involving prisoners, the IRB must (1) determine that the research satisfies a number of general requirements and (2) provide protocol-specific documentation that the research meets the specific criteria for one of four permitted categories.
- Both DHHS and FDA human subjects regulations require special protections for the participation of children in research.
- Important issues for IRBs to consider when reviewing research involving children include the risk-benefit analysis, provisions for parental permission and child assent, and protocol-specific documentation that all of the criteria of one of four permitted categories have been satisfied.
- Employees, former employees, and students all share the disadvantage of residing at the lower, vulnerable end of a significant power relationship and require protections similar to those provided to vulnerable populations.
- Economically disadvantaged persons may be particularly vulnerable to undue influence related to accepting financial incentives that may accompany research participation.
- Although protectiveness may be a natural tendency that occurs when enrolling mentally ill or mentally disabled persons in research, persons with mental illness, advocates for the mentally ill, and mental health professionals argue forcefully that mental illness does not necessarily result in a complete inability to make autonomous choices.
- IRBs should obtain information regarding laws and science that bear on the decisionmaking capacity of any potentially vulnerable populations that may be involved in proposed research.
- It is essential for IRBs and research investigators to understand and strictly observe state laws regarding the authority of legally authorized representatives to provide consent for research participation.

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Chapter 22

Disclosing and Managing Conflicts of Interest

- A. Introduction
- B. Background of Concerns About Conflicts of Interest
- C. The Common Rule and Conflicts of Interest
- D. Public Health Service Regulations
- E. Food and Drug Administration Regulations
- F. Department of Health and Human Services Guidance
- G. Other Policy Statements on Conflicts of Interest

Key Concepts

References



A. Introduction

Financial relationships or other factors that could affect individual or institutional judgment should not compromise any of the fundamental ethical principles of research with human subjects—respect for persons, beneficence, and justice (National Commission 1979). Concerns arise when financial or other considerations (e.g., promotions, tenure, publications) compromise—or have the appearance of compromising—the professional judgment of the investigator, Institutional Review Board (IRB), or the institutional official; independence in the design, conduct, and publication of research; and/or the welfare of human subjects. When professional judgment is swayed by financial or other interests, subjects can be harmed by, for example, being exposed to study designs that pose unacceptable risks, enrolling subjects in studies inappropriately, or continuing studies that should be modified or stopped.

Openness and honesty are indicators of respect for persons; thus, when possible conflicts arise between the need to protect subjects by minimizing risks and the desire for financial or other gain, these conflicts must be disclosed and managed. Although disclosure might encourage investigators to think carefully before agreeing to arrangements that pose conflicts or that might provide others, such as institutional officials, an opportunity to assess the risks and potential benefits of financial arrangements, it is not an

absolute solution. Organizations, particularly academic institutions, should actively manage investigators' financial conflicts and increase their self-regulation efforts in this area.

This chapter describes the background and evolution of conflicts of interest regulations and guidance and summarizes existing positions on this complex issue.

B. Background of Concerns About Conflicts of Interest

As early as 1978, the potential for conflicts of interest in research was noted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission), which wrote that “investigators are always in positions of conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research” (National Commission 1979). Concern about conflicts was one reason the National Commission recommended independent review of all research protocols. Thus, IRB assessment of research has evolved as one method for identifying and dealing with conflicts of interest that investigators might face in the conduct of human subjects research. More recently, however, institutions have formed separate conflicts of interest committees that specifically focus on these issues in the context of research.

At the time of its deliberations, the National Commission recognized that conflicts can be other than financial and that successful research also creates less tangible benefits, such as prestige, power, and promotion. In fact, the desire for professional advancement, fame, or to make a scientific breakthrough can constitute very strong conflicts of interest. However, in the past 25 years, as the biomedical research environment has increasingly provided opportunities for investigators and institutions to profit monetarily from research, the focus on financial conflicts of interest has increased. In addition, financial interests are more tangible and easier to address than intellectual bias or desire for recognition.

Prior to 1980, government conflicts of interest restrictions were narrow and limited to the commercialization of inventions developed at research universities with the support of federal funds. With the passage of the Bayh-Dole Act in 1980,¹ recipients of federal dollars were allowed to retain the ownership of their patents. The act encourages grantees to seek commercial use of federally financed inventions, primarily through collaborations with small businesses. The Stevenson-Wydler Technology Innovation Act,² also signed in 1980, created similar rights and expectations for government research agencies, such as the National Institutes of Health (NIH). These laws and subsequent amendments have resulted in substantial increases in the transfer of technologies among universities, government, and the private sector in the United States. In the area of human research, many of these activities involve clinical drug trials, which are typically funded by the manufacturer of the product being studied.

These increasingly common financial arrangements are complex and are not inherently unethical. Additionally, not all financial interests cause conflicts of interest or pose potential harm to subjects. However, to the extent that financial interest may affect the rights and welfare of human subjects in research, IRBs, institutions, and investigators need to consider what actions may be necessary to protect subjects.

Conflicts of interest could cloud an investigator's judgment about the risks and benefits associated with research participation and may lead to subjects not receiving full and objective information about the study. These concerns led in the late 1990s to renewed and increased attention to conflicts of interest policies, which continue to evolve. In general, public and private policies have increasingly emphasized the view that IRB review alone is not sufficient to manage financial conflicts, because the options available to IRBs to eliminate such conflicts are limited. Policy discussions generally note that IRBs should not be

the primary conflict of interest review body for reasons other than their limited recourse, including the following:

- IRBs do not have conflicts of interest review as a primary mandate
- IRB membership is thus constituted differently than one would constitute a conflicts of interest review committee
- institutional processes need to capture all forms of research (basic, as well as clinical) and even other professional activities, which represents a much broader scope than is included under the IRB's purview

C. The Common Rule and Conflicts of Interest

Several aspects of the Common Rule incorporate mechanisms for assessing and managing conflicts of interest, the most obvious being the need for independent review of research.

Conflicts of Interest for Investigators and Disclosure.

Investigators' financial conflicts of interest could include capitated payments or bonuses for enrolling participants, indirect payments through consultantships or honoraria, and equity holdings in companies or royalties from patents whose value may be affected by the research.

IRBs should be aware of investigators' financial arrangements relevant to research under review (e.g., company ownership, stock options, consulting fees). Until recently, most academic medical centers only required investigators to disclose such financial interests

*investigators'
financial
arrangements*

to a university official or to a committee but not to the IRB. Knowledge of the presence of financial conflicts of interest for the investigator might affect an IRB's assessment of the protocol in its entirety and whether the research should be approved, or it might affect its assessment with respect to the amount or type of monitoring needed. At some institutions, a conflicts of interest review committee examines financial interests relevant to the study and determines whether any conflicts exist and how they should be managed. Only those interests that create potential bias and therefore lead to some "conflict management" arrangement or balancing bias among IRB members are then reported to the IRB in order to ensure that potential risks to subjects are adequately addressed under the arrangement.

One area in which an IRB must be involved is determining what information about financial conflicts of interest

¹ See www4.law.cornell.edu/uscode/html/uscode35/usc_sec_35_00000200----000-.html.

² See <http://www.csrees.usda.gov/about/offices/legis/techtran.html>.

should be shared with research subjects as part of the informed consent process. In 2001, the National Bioethics Advisory Commission (NBAC) examined conflicts of interest issues in its report *Ethical and Policy Issues in Research Involving Human Participants*. NBAC's discussions highlighted a number of concerns surrounding the issue of disclosure, primarily related to the privacy of investigators and the relevance and understandability of the information to potential subjects. Potential subjects clearly need to understand the nature of the research study in which they might participate, including who is likely to benefit from it, as well as the prospect that financial benefits that might accrue to investigators. NBAC concluded that although necessary, disclosure by investigators to subjects of financial and potentially conflicting interests should not serve as a substitute for the institutional management of conflicts of interest.

In addition, disclosure to the institution or the IRB, although often important, may not be either necessary or sufficient for managing and resolving these issues. Presumably, if the investigator has a concerning financial interest, the research institution should have dealt with the interest in some acceptable way prior to the stage where subjects are undergoing the informed consent process. Finally, nonconcerning financial interests presumably are not relevant to risks to subjects and will be of questionable value in the subject's risk-benefit calculus.

disclosure to the institution or the IRB

Conflict of Interest for IRB Members. IRB members are prohibited from participating in any deliberative discussion or vote related to any research in which they have (or may appear to have) a financial, personal, or professional conflict (§____. 107(e)). Food and Drug Administration (FDA) IRB regulations include exactly the same provision. An IRB member who has a financial stake in the research or plays a substantive role in the research (including, e.g., enrolling subjects in the protocol) would be considered to have a conflict of interest. IRBs are required to manage the conflicts of interest of their members.

The Office for Human Research Protections (OHRP) interprets the Department of Health and Human Services (DHHS) regulations to prohibit IRB members from participating in any deliberative discussion or vote that is related to any research in which they participate in any way, including but not limited to study planning and design, the conduct of the study, data analysis, subject recruitment, subject consent, and authorship. If the IRB member believes that he/she has a conflicting interest that might affect, or appear to affect, IRB deliberations or the protection of human subjects, the member should declare the presence of the conflict to the

IRB and recuse him/herself from the deliberations and vote on such research. In some cases, the IRB might ask the conflicted member to leave the room during a vote or during critical discussions.

If the conflict of interest is nonfinancial and the individual recuses him/herself from discussion, then, in general, disclosure of the nature of the interest might not be necessary (but in some cases it might be advisable). There may be circumstances in which it is in the best interests of the individual, the institution, and/or the human subjects involved for the member to make a complete, written disclosure to the conflicts of interest official or committee. IRB members are expected to use their best judgment to ensure that all IRB deliberations take place without any appearance or possibility of conflict of interest.

At the institutional level, conflicts of interest can include equity holdings in companies and the economic benefits of patents they hold. To prevent the IRB from representing solely an institutional viewpoint, the IRB must include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution (§____. 107(d); 21 CFR 56.107(d)).

These two conditions for managing conflicts of interest—recusing conflicted IRB members and ensuring unaffiliated membership on the IRB—reflect concerns about the personal conflicts of individual IRB members and the conflicts an IRB may have as part of the institution.

D. Public Health Service Regulations

Since 1995, specific regulations have been in place in some federal agencies regarding conflicts of interest, specifically Public Health Service (PHS) agencies and the National Science Foundation (NSF). Each institution that applies for a research, research training, or research-related grant or cooperative agreement under the Public Health Service Act must certify that the institution has established administrative policies as required by the 42 CFR Part 50, Subpart F, "Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is sought."³ Institutions receiving support from NSF must meet identical requirements.

42 CFR Part 50, Subpart F

The PHS regulations (see Table 22.1) require that institutions establish policies and procedures relating to the disclosure and management of financial conflicts of interest

³ See http://grants1.nih.gov/grants/compliance/42_CFR_50_Subpart_F.htm.

Table 22.1

PHS Financial Conflicts of Interest Regulations at 42 CFR Part 50, Subpart F

Significant financial interests must be disclosed by researchers to their institutions.

These include

- anything of monetary value, including but not limited to:
 - salary and other payments for services (i.e., consulting fees or honoraria)
 - equity interests (i.e., stocks, stock options or other ownership interests)
 - intellectual property rights (i.e., patents, copyrights, and royalties from such rights)

Significant financial interest does not include

- salary, royalties, or other remuneration from the institution for purposes unrelated to the research in question
- income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities
- income from service on advisory committees or review panels for public or nonprofit entities
- an equity interest that when aggregated for the investigator and the investigator's spouse and dependent children does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value and does not represent more than a 5 percent ownership interest in any single entity
- salary, royalties, or other payments that when aggregated for the investigator and the investigator's spouse or dependent children over the next 12 months are not expected to exceed \$10,000
- ownership in a Small Business Innovation Research Program, as defined by DHHS

Management plans might include

- public disclosure of financial interests;
- monitoring of the research by independent reviewers;
- modification of the research plan;
- complete divestiture of interests in the sponsor, product, or entity under study;
- selection of another investigator or research staff person to perform the research or research-related function;
- disclosure of the conflicting interest in the informed consent document and any manuscripts or oral presentations based upon the research in question and severance of relationships that create actual or potential conflicts.

for researchers, their spouses, and their dependent children. Once a significant financial interest has been disclosed by a researcher, it is up to the institutional conflicts of interest official (or committee) to determine whether the disclosed financial interest requires management. The IRB should be notified of any conflict affecting personnel involved in human subjects research. Any proposed management plan must be determined by the IRB to be satisfactory from a human subjects protection perspective.

E. FDA Regulations

FDA regulations at 21 CFR Part 54⁴ govern *individual investigator* disclosure of financial conflicts of interest to sponsors of FDA-regulated research (see Table 22.1). These regulations require that investigators disclose information related to conflicts of interest (for themselves, their spouses,

and their dependent children) to the research sponsor so the sponsor can inform FDA. As such, they differ slightly from the DHHS regulations, in that they require disclosure of certain financial interests above a certain amount, regardless of whether they constitute a conflict of interest. Most institutions require investigators to provide copies of all disclosures provided to sponsors to the conflicts of interest official or committee.

If there are no financial interests or arrangements between the sponsor and the investigator (or the investigator's spouse or dependent children), an investigator certifies this fact to the sponsor who, in turn, provides this certification to FDA using a Form FDA 3454. Financial interests or arrangements are disclosed using a Form FDA 3455, as are any steps taken to minimize the potential for bias.

⁴ See www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=54&showFR=1.

Information submitted to the sponsor or FDA must be updated by the investigator whenever there is a change in the information during the study and for one year after its completion.

The obligation to provide information to FDA related to conflicts of interest usually belong to the sponsor of the research. When an individual investigator holds the Investigational New Drug Application or the Investigational Device Exemption, that investigator is classified as a sponsor-investigator who must fulfill the same obligations that an outside sponsor would have to fulfill.

Sponsors are required to disclose certain financial interests of clinical investigators to FDA in marketing approval applications under the Federal Food, Drug and Cosmetic Act (21 CFR part 54). FDA regulations at 21 CFR Part 54 address requirements for the disclosure of certain financial interests held by clinical investigators. The purpose of the current FDA regulations is to provide additional information to allow FDA to assess the reliability of the clinical data (21 CFR 54.1). The FDA regulations require sponsors seeking marketing approval for products to certify that investigators do not have certain financial interests or to disclose those interests to FDA (21 CFR 54.4). These regulations require sponsors to report (1) financial arrangements between the sponsor and the investigator whereby the value of the investigator's compensation could be influenced by the outcome of the trial; (2) any proprietary interest in the product studied held by the investigator; (3) significant payments of other sorts over \$25,000 beyond costs of the study; or (4) any significant equity interest in the sponsor of a covered study (21 CFR 54.4).

F. DHHS Guidance

On May 12, 2004, DHHS announced a final guidance document for IRBs, investigators, research institutions, and other interested parties. *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection* raises points to consider in determining whether specific financial interests in research could affect the rights and welfare of human subjects and, if so, what actions could be considered to protect those subjects. It recommends that, in particular, IRBs, institutions engaged in research, and investigators should consider whether specific financial relationships create financial interests in research studies that may adversely affect the rights and welfare of subjects. More detailed points for consideration are also offered for institutions, IRBs, and investigators. This docu-

ment does not create or confer rights for or on any person and does not operate to bind DHHS, including FDA, or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes and regulations. This guidance applies to human subjects research conducted or supported by DHHS or regulated by FDA.

The guidance presents a single DHHS-wide reference point for decisionmaking that would apply to all human subjects research conducted or supported by DHHS and its agencies. It would also apply to all human subjects research regulated by FDA. The document is nonbinding and does not change existing regulations or requirements or establish new ones.

According to the guidance, an institution or an individual involved in human research may ethically hold financial relationships related to or separate from particular research projects. These relationships may result in financial interests of monetary value, equity interests, or intellectual property rights. A potential conflicting financial interest is one that will create, or may be reasonably expected to create, a bias stemming from that financial interest. In severe cases, these conflicts of interest may potentially or actually affect the rights and welfare of research subjects.

IRBs, institutions, and investigators involved in human subjects research all have roles in ensuring that financial interests do not compromise the protection of human subjects. The DHHS guidance is divided into sections focused on recommendations for institutions, IRB operations, IRB review, and investigators. After a section of suggested questions that each of these entities might pose in considering the existence of possible conflicts of interest, the final section of the guidance provides suggested actions aimed at eliminating or reducing financial conflicts.

The guidance recommends that institutions consider the following actions aimed at reducing or eliminating conflicts of interest:

- separating the responsibility of financial decisions from research decisions
- establishing a committee to assess potential individual or institutional conflicts of interest
- establishing criteria to determine what constitutes conflicts of interest
- establishing clear communication guidelines between the conflicts of interest committee and the IRB as well as procedures for the provision of information and the recording of findings of conflicts of interest committees
- further separation of financial oversight and training of staff

In terms of IRBs, the guidance recommends consideration of the following actions:

- determining whether methods being considered or used for the management of financial interests of the parties involved in the research adequately protect the rights and welfare of human subjects, or whether the IRB needs additional information to determine this
- determining what actions are appropriate in order to minimize risks to subjects
- determining the type, amount, and level of detail to be provided to the subject regarding the sources of funding and financial interests of the investigator and/or the institution

The recommendations for investigators require that the investigator consider the potential impact that a financial relationship of any kind might have on a clinical trial—including relationships with subjects—and consider whether to take any of the following actions:

- include information on the consent form that describes the details of funding arrangements
- use special measures to obtain consent, including the use of a nonbiased third party
- consider establishing an independent data monitoring board

There may be cases in which, despite these additional controls, the research study would be more safely performed by another investigator or at another location.

G. Other Policy Statements on Conflicts of Interest

Several national bodies have reviewed conflicts of interest issues over the past decade. Although recommendations made by these groups are advisory only, the deliberations of these groups can serve to highlight some of the more contentious issues regarding policies and practices in this area.

As mentioned earlier, NBAC examined conflicts of interest issues in its 2001 report *Ethical and Policy Issues in Research Involving Human Participants*. NBAC recommended that Common Rule guidance provide definitions for institutional, IRB member, and investigator conflicts of interest. NBAC also recommended the issuance of guidance addressing how institutions, IRB members, and investigators can manage conflicts of interest to ensure adequate protection of research subjects. One such protection includes disclosure in the informed consent document of institutional, IRB-related, and investigator financial interests and arrangements to potential subjects.

In a 2003 report, *Responsible Research: A Systems Approach to Protecting Research Participants*, an Institute of Medicine (IOM) committee wrote that IRBs should not bear the primary responsibility for identifying and managing financial conflicts of interest, as they lack the necessary resources, expertise, or authority to do so (IOM 2003). However, the IOM report noted that the most “important function in assessing potential conflicts of interest (financial or nonfinancial) in human research studies is determining whether bias or overly optimistic promises of potential benefits are clouding risk assessments” (82). Thus, the IRB should retain a central role in determining whether financial conflicts of interest have the potential to affect subject safety, and, if necessary, how subjects should be informed of any resulting risk.

The IOM committee stated that potential financial conflicts of interest of the investigator, IRB members, or the institution should be assessed by the organization’s relevant conflict of interest oversight mechanism and communicated to the IRB. The IOM committee focused only on financial conflicts of interest and recommended that a conflict of interest oversight body determine whether financial conflicts should be disclosed or managed or are so great that they compromise the safety or integrity of the proposed research. According to the 2003 IOM report:

The conflict of interest body should communicate to the IRB its determination of potential conflicts relevant to protecting the rights and welfare of research participants, the rationale for its determination, and any recommended conflict management plan. The IRB should use this information to determine if and how subject protection could be negatively affected, whether the recommended conflict management plan is sufficient to ensure subject protection, what information pertaining to any conflict should be disclosed to research subjects through the informed consent process, and whether ongoing review is required in the event that the research goes forward (74).

Other influential groups also have weighed in on this issue. In a 2001 report, *Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*, the American Association of Medical Colleges (AAMC) advised that careful review of investigator financial interests is needed to protect research subjects. Research should not be approved or undertaken until an investigator can rebut the presumption that a financial interest is problematic. AAMC endorses the development of comprehensive, unambiguous, and consistently enforced policies and

procedures and the implementation of management methods that are transparent to the research community and the public at large.

AAMC also addresses *institutional* financial conflicts of interest in *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research* (2002). As a fundamental principle, AAMC recommends that the functions and administrative responsibilities related to human subjects research be separated from those related to investment management and technology licensing.

In addition, AAMC points out that circumstances exist in which separation of function is not sufficient to avoid the appearance of institutional conflicts of interest. Where such circumstances exist, the human subjects research should not be conducted at (or under the auspices of) the institution with the conflict, absent compelling circumstances and careful management of the conflict.

The Association of American Universities (AAU) also has developed guidelines for managing both individual and institutional financial conflicts of interest in its *Report on Individual and Institutional Financial Conflict of Interest* (2001). Guidelines for *individual* conflicts of interest focus on disclosure and review processes and generally do not allow related financial interests in research involving humans except in compelling circumstances.

AAU guidelines for *institutional* conflicts of interest recommend a three-fold approach as follows:

1. *Disclose* always
2. *Manage* the conflict in most cases
3. *Prohibit* the activity when necessary to protect the public interest or the interest of the institution. A key goal is to segregate the decisionmaking about financial activities from the research activities so that they are separately and independently managed.

Key Concepts: Disclosing and Managing Conflicts of Interest

- For the purpose of this discussion, a conflict of interest can be defined as any situation in which financial, professional, or personal obligations may compromise or present the appearance of compromising an individual's professional judgment in designing, conducting, analyzing, or reporting research.
- PHS regulations address how institutions receiving PHS or NSF support should handle financial conflicts of interest.
- FDA regulations govern individual investigator disclosure of financial conflicts of interest to sponsors of FDA-regulated research.
- NBAC recommends disclosure of institutional, IRB-related, and investigator financial interests and arrangements to potential subjects in the informed consent document.
- AAMC recommends that research not be approved or undertaken until an investigator can rebut the presumption that a financial interest is problematic. AAMC also recommends that the functions and administrative responsibilities for human subjects research be separated from those for investment management and technology licensing. When this is not sufficient to avoid the appearance of conflicts of interest, the research should not be conducted at (or under the auspices of) the conflicted institution, absent compelling circumstances and careful management of the conflict.
- AAU guidelines for individual conflicts of interest focus on disclosure and review processes and generally do not allow related financial interests in research involving humans except in compelling circumstances. AAU guidelines for institutional conflicts of interest recommend the following: (1) disclose always, (2) manage the conflict in most cases, and (3) prohibit the activity when necessary. The goal is to segregate the decisionmaking about financial activities and the research activities.
- IRB members are prohibited from participating in the deliberative discussion or voting related to any research in which they participate in any way, including, but not limited to, study planning and design, conduct of the study, data analysis, subject recruitment, subject consent, and authorship. IRB members are likewise prohibited from participating in the deliberative discussion or voting related to any research in which they have (or may appear to have) a financial, personal, or professional conflict.
- DHHS has issued guidance, *Financial Relationships and Interests in Research Involving Human Subjects*, presenting a single DHHS-wide reference point for decisionmaking that would apply to all human subjects research conducted or supported by DHHS and its agencies. It would also apply to all human subjects research regulated by FDA. The document is nonbinding and does not change existing regulations or requirements or establish new ones.
- According to the DHHS guidance, an institution or an individual involved in human research may ethically hold financial relationships related to or separate from particular research projects. A potential conflicting financial interest is one that will or may be reasonably expected to create a bias stemming from that financial interest.
- The DHHS guidance emphasizes that IRBs, institutions, and investigators involved in human subjects research all have roles in ensuring that financial interests do not compromise the protection of human subjects.

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Chapter 23

Accreditation and Quality Assurance of Human Research Protection Programs

- A. Introduction
 - B. Accreditation
 - C. Quality Assurance
- Key Concepts**



A. Introduction

As described in Chapters 1 through 3, after several decades of debate, the fundamental tenets of what constitutes ethical human subjects research emerged as the regulatory framework that is in existence today. Increasing focus on the effectiveness of the human research oversight system raised concerns about the ability of institutions to effectively and consistently comply with the regulatory requirements. As a result, toward the end of the 1990s, the concept of accreditation programs emerged as a potential mechanism for measuring compliance of human research protection programs (HRPPs) within a set of standards. Accrediting programs, which are generally voluntary and represent a profession's desire to self-regulate, are widely used in the fields of health care and education and are viewed as having a major and generally positive influence. Many accrediting programs strive to meet higher standards than are required by law; thus, having the credential can imply a higher level of competence than what may be minimally required.

However, accrediting programs can also have a one-size-fits-all approach. That methodology works well for vetting HRPPs of similar size, scope and volume; but, such a gauge doesn't always measure up for HRPPs with uncommon

projects, subject pools, sponsors, and classified or restricted information.

Programs of self-assessment and review by an external group, such as that offered by the Office for Human Research Protections (OHRP), are an option for programs seeking a more tailored approach to quality improvement.

B. Accreditation

Currently, the Association for the Accreditation of Human Research Protections Programs (AAHRPP) is the primary accrediting body of Human Research Protection Programs in the United States. It was founded by seven non-profit organizations that represent the leadership of universities, medical schools, and teaching hospitals; biomedical, behavioral, and social scientists; IRB professionals; and patient and disease advocacy organizations.

**Accreditation of
Human Research
Protection
Programs**

Based on nine guiding principles, AAHRPP has developed a set of accreditation standards and procedures¹ across three domains: organization, IRB or ethics committee, and researcher and research staff.

¹ The AAHRPP accreditation process and the standards can be viewed at www.aahrpp.org.

The first step in earning AAHRPP accreditation is an extensive self-assessment. Once completed, the review materials are submitted to AAHRPP. A team of experts reviews the self-assessment materials and schedules an on-site visit. Site visitor teams are typically comprised of three or four individuals who represent different perspectives with regard to the research enterprise: those of the IRB, the researcher, and the institution, as well as the public/participant perspective. During the visit, the team evaluates the program's performance with respect to AAHRPP's accreditation standards.

AAHRP's process has four possible outcomes:

1. Full Accreditation
2. Qualified Accreditation
3. Accreditation Pending
4. Accreditation Withheld

For more information, visit AAHRP's web site.²

Another organization, Alion Science, was selected by the VA in 2012 to accredit all VA facilities conducting human subjects research. More information on the Alion Science program can be found at: <http://www.research.va.gov/pride/accreditation/default.cfm>.

C. Quality Assurance

OHRP offers an alternative to accreditation that combines use of a self-assessment instrument and voluntary submission to a comprehensive review by members of the OHRP Education Division. Institutions also can arrange for an external review using the OHRP Quality Assurance (QA) consultation approach and tools. OHRP will even train officials of Common Rule agencies in conducting a QA consultation using the OHRP approach.

OHRP offers a variety of resources to help institutions evaluate and strengthen the quality of their human research protection program.

Through direct consultation, in-person or via a video or phone conference, OHRP:

- Clarifies regulatory requirements;
- Provides detailed review of IRB written procedures and meeting minutes;
- Explores ways to improve the quality, efficiency, and effectiveness of IRB administration; and
- Identifies "best practices."

OHRP can also:

- Foster partnerships and collaborations among institutions.
- Conduct a training session addressing human subject protections issues on-site at an institution, or via video teleconference.

² See www.aahrpp.org.

Key Concepts:

Accreditation and Quality Assurance of HRPPs

- Accreditation is one approach to improving the human research protection system.
- A comprehensive quality improvement program examining the operation of the HRPP within an organization can perform many of the same functions achieved through accreditation.
- Accrediting programs are widely used in the fields of health and education.
- Accreditation programs generally involve experts and peers developing a set of standards that represents a consensus of the best practices in the profession.
- Neither accreditation nor quality assurance programs obviate the regulatory responsibilities of 45 CFR 46 or FDA requirements. In addition, neither has meaning in terms of eligibility for receiving federal research funding.

Chapter 24

Guidance for Genetic Research

- A. Introduction
 - B. Research with Individuals
 - C. Research Involving Families
 - D. Research Involving Specific Populations or Communities
 - E. Genetics Research with Stored Samples or Information
- Key Concepts**
References
Appendix 24.A: Glossary



A. Introduction

The collection and analysis of genetic data have been fundamental components of human subjects research for some time. When developing and reviewing protocols that include genetics or genomics research,¹ it is important for investigators and Institutional Review Boards (IRBs) to recognize that this type of research poses few strictly novel or unique risks to subjects yet offers the potential to advance scientific understanding of disease and lead to the development of new tools to improve clinical care and treatment options. Within the realm of biomedical science, there is a broad spectrum of genetics questions that may be pursued, ranging from the study of a fully penetrant² single-gene disorder to the examination of the nonheritable genetic underpinnings of common cancers. In addition, there are epidemiologic studies of conditions diagnosed by cytogenetic, molecular, biochemical, metabolic, or clinical findings, as well as social science studies examining the effect of genetic technologies or genetic information on individual or group perceptions.

Neither genetics studies nor the resulting genetic information should be isolated as unique domains within

research. IRBs should welcome proposals that include genetics research and evaluate and monitor these projects as they would any other type of project—that is, through the application of reasonable human subjects protections appropriate to the risks and benefits presented by each individual proposal.

This chapter highlights issues that require attention when applying the longstanding principles of human subjects protections to genetics research, which has some notable attributes (see Table 24.1). If IRBs apply these protections in a thoughtful and reasonable manner, human subjects should benefit from the research with very little risk of harms. As breakthroughs in basic genetics research continue to accelerate the advent of genomic medicine and expand the opportunities to individualize clinical options, the demand for—and demands on—clinical research will significantly increase. While the potential benefits of this research for society are great, the obligation of the IRB is to the research subject, and its consequent duty is to balance the specific risks and benefits for the individual subject. This chapter focuses on defining and exploring the potential benefits and risks commonly presented by genetics studies. More important, the goal of this chapter is to provide guid-

¹ *Genetics* is the study of individual genes and their functions, while *genomics* is the study of the activity and interactions of the full complement of genetic information. However, for the purposes of this chapter *genetics research* is presumed to include both genetics and genomics studies, unless otherwise stated.

² A glossary with definitions for frequently used genetics terminology can be found at the end of this chapter.

Table 24.1
Aspects of Genetic Information That May Require Consideration

- Genetics research often requires gathering data on relatives who may not be enrolled in the research study.
- Knowledge of an individual's inherited genetic status may allow one to predict the genotypes of their blood relatives.
- Genetic information (like many biomarkers) may have either highly predictive or ambiguous value for the subject.
- Genetic information may have significant cultural importance for some subjects or communities, which may influence their understanding of research results.

ance on practical approaches to avoid or minimize harms and ways to clarify the nature and (apparently low) magnitude of these risks to the subjects.

In most cases, an IRB that includes scientists, clinicians, and laypersons will be able to address the human subjects considerations of a genetics or genomics protocol without seeking additional ad hoc expertise. However, in some situations, discussed below, issues may arise for which additional expertise in genetics or the ethics of genetics research may be appropriate in order to complement specific gaps in an IRB's experience.

Considerations of Research Design

With the exception of gene transfer research,³ current genetics research usually poses minor physical risks to subjects that are associated with the acquisition of samples (e.g., a blood draw or buccal sample) or clinical tests (e.g., MRI scans, ultrasounds). Anticipated risks are more likely to involve the psychological and social consequences of the information generated, collected, or analyzed (e.g., loss of genetic privacy, stigmatization, diminished insurability and employability). In order to assess the nature of such risks in the context of the potential benefits within a specific protocol, it can be useful for the IRB to consider several questions, as follows, about the design of a study in its initial analysis:

- Does the investigator plan to return individual research findings to subjects?
- Will information regarding family members be collected in the course of the research (e.g., through the generation of pedigrees)?
- Will specific populations or defined communities be sought for the research?
- Will tissue or genetic information be stored for future use?

Study design choices that address issues involving the collection of potentially sensitive information can minimize or eliminate many of the potential risks associated with genetics research. Additionally, the most significant risks of

genetics research are often relevant only if individual research findings are returned to subjects. Therefore, if studies can be scientifically and ethically designed to not include the reporting of individual research results to subjects, many of the concerns and subject protection needs detailed in this chapter will not be applicable. However, there are issues associated with genetics research with families, specific populations, and stored samples (or information) that should be considered regardless of the decision to return research results to subjects. These issues are discussed separately below.

B. Research with Individuals

General Risks and Benefits Associated with Genetics Research

Genetics research at a basic level, such as genome sequencing or building haplotypes, generally offers no direct benefit to subjects. However, when direct benefits are offered to subjects or there is an expectation of receiving such benefits, the issues involved with incentives should be considered. For example, studies that return individual research findings to subjects may be perceived by the individual or others to offer personal (or family) benefits. Similarly, studies that offer commercially available genetic tests at no cost to the subject may represent a financial incentive for participation (similar to possible perceived benefits for other costly medical tests provided through research protocols).

In many genetics studies, potential nonfinancial incentives are more likely to exist than possible financial incentives. Research subjects may believe that genetic information will provide long-awaited hope toward understanding a condition in their family and, ultimately, access to improved treatment, cure, or more informed family planning. Therefore, the offer to provide research-related individual findings to subjects may motivate them to consent to research based on a perceived expectation of direct benefit. In such instances, research goals should be clearly distinguished from poten-

³ See Chapter 25 for an in-depth discussion of the relevant risks, benefits, and other considerations pertinent to overseeing gene transfer research.

tial direct benefits in the informed consent process (preceding and during study conduct) to ensure an accurate understanding of the likely utility and validity (or lack thereof) of the genetic information to be generated (see discussion below). This is particularly important when enrolling individuals with life-threatening genetic conditions, as they may be more likely to perceive, consciously or unconsciously, that their participation in genetics research may have a direct benefit. The relevant issues to consider in such situations are similar to those in many other areas of medical research in which investigators should exercise particular caution to avoid a therapeutic misconception among enrolled subjects (e.g., Phase 1 oncology trials).

Just as basic genetic research typically offers little benefit to human subjects, it typically poses harms that are of very low frequency or consequence. Yet, when individual results are returned, there can be potential harms. The potential psychological harms of learning about one's genetic status, risk for disease, or biological relationship to relatives⁴ include undesired changes in feelings, thoughts, or beliefs that can lead to stress, anxiety, or depression (see Table 24.2). The effects of these harms may be transient or persistent (Beauchamp and Childress 2001; Marteau and Lerman 2001). If a study protocol includes the act of returning individual findings to the subjects, the investigator and IRB should determine whether genetic counseling services should be provided as part of the protocol and whether referrals to medical or counseling services are appropriate during the informed consent process. In many cases, if there is a determination that there are potential harms of this nature, provision of appropriate medical and genetic counseling services may markedly mitigate such risks.

The social risks of participating in genetics research that generates information regarding an individual's potential susceptibility for disease or illness include the possibility of genetic discrimination or stigmatization (Beauchamp and Childress 2001).⁵ Although this harm is likely to be rare, reasonable privacy and confidentiality protections should be in place to minimize the chances for a breach of such information to occur. However, even a subject's personal knowledge of individual disease risk based on research results leaves them vulnerable to potential discrimination. For example, if an insurer inquires about a subject's knowledge of a particular disease risk, the subject is required to be forthcoming with known information and therefore risk increased insurance costs or limited coverage. Although neither the absolute or relative risk of genetic discrimination has been well documented, it is a potential harm, and research protocols should include reasonable methods to minimize any associated risks (e.g., defined disclosure and confidentiality procedures).

privacy and confidentiality protections should be in place

When investigators submit protocol renewals or when IRBs conduct periodic reviews, the protocol assessment should include an explicit evaluation of whether new scientific evidence has emerged that may alter the risk-benefit analysis relative to the original review. For example, the original studies examining ApoE mutations in subjects were intended to increase understanding of hyperlipidemia (de Knijff et al. 1994). Yet, investigators later learned that alterations to the ApoE allele were in some cases relevant to an individual's predisposition to develop Alzheimer's disease (Strittmatter and Roses 1995). Uncovering such information in the course of research and the necessity of communicating findings to research subjects should be considered not only for subjects currently enrolled in a study but also those who have participated in the past.

Table 24.2

Potential Psychosocial Risks Related to Learning Individual Research Results

- Distressing changes in thoughts, beliefs, or self-perception based on the real or perceived meaning of genetic information
- Altered or stressed family relationships
- Individual (or group) stigmatization based on real or perceived meaning of genetic information
- Discrimination based on genetic information (e.g., in insurance or employment contexts)
- The psychological effect of information with limited clinical validity and/or utility

⁴ Common professional practice among research investigators is not to share information uncovered regarding misattributed familial relationships unless it substantially alters recurrence risk or clinical management.

⁵ The Genetic Information Nondiscrimination Act of 2005 (S. 306) was approved by the Senate on February 17, 2005. A separate bill (H.R. 1227) was introduced in the House of Representatives by Congresswoman Judy Biggert. Many states have also passed genetic nondiscrimination legislation. See www.genome.gov/PolicyEthics/LegDatabase/pubMapSearch.cfm.

Returning Individual Research Results to Subjects

Some have argued that not returning individual research results to subjects is unjustifiably paternalistic and that research subjects should be fully informed about research results they might consider relevant to their situation or condition (De Witte and Have 1997; Moreno 2001). Counter-arguments state that this is only true when sufficient data have been collected to validate the meaning of the finding and that the investigators should provide a clear assessment of the potential risks and benefits to the subject based on the investigator's knowledge (Annas 2001). Inadvertent harm may occur as knowledge about the implications of carrying a specific genotype evolves and as initial interpretation of results may prove incorrect. For example, a review of the history of breast cancer susceptibility testing shows that risk estimates associated with particular genotypes changed significantly during the first 10 years of this work (Easton et al. 2004).

As noted earlier, IRBs and investigators should keep in mind that many of the potential harms reviewed above are only relevant if individual research results are to be returned to subjects. Therefore, when reviewing genetics or genomics protocols, one of the primary questions IRBs should consider is the necessity and utility of whether and if so how to share *individual* research findings with subjects. It is important to distinguish studies that have high predictive power and thus offer valid information or a potential direct benefit to an individual subject from those that have significance only at the population or group level. Of course, considerations of benefits must be balanced with potential risks of harm, including psychosocial risks (Beauchamp and Childress 2001; NBAC 2001; Prentice and Gordon 2001). For example, a study that shows a 25 percent increase in the population risk of coronary artery disease in a group with a particular allele is important and will contribute to understanding a common health problem. However, this study might have poor predictive value for any given individual in cases in which such variables as body weight, lipid levels, exercise, and diet make the genetic prediction alone weak. In these instances, the research subjects may not benefit from obtaining their specific results and may in fact suffer unwarranted anxiety. In contrast, research on rare disorders may include genetic testing, and, if appropriate conditions such as Clinical Laboratory Improvement Amendments (CLIA) certification of the laboratory are in place, the return of individual findings might confer some direct benefit to the subject in terms of providing a diagnosis or recommending appropriate clinical follow-up (see further discussion below).

Studies that do not return individual genetic information to subjects may still confer indirect benefits to subjects. Subjects may perceive research participation as a productive or valuable contribution to society, and they may draw satisfaction from the hope that others with the same condition may ultimately benefit from the research. Although this motivation resembles the altruistic benefit of participating in medical research generally, it may be confounded with the hope or desire that one or, particularly in genetics research, one's relatives may directly benefit from the research in the future. This hope can be a particularly strong motivating factor if there is no treatment or standard of care for the condition under study. An example in which hope for personal benefit might influence a potential subject occurs when contact information for subjects is placed in a registry and the subjects are flagged as willing and available for additional studies related to the condition that affects their families.⁶ Subjects may perceive the possibility of future contact as a benefit of participation, even without the prospect of learning information specific to their own conditions (Appelbaum et al. 1987; Dresser 2002). Such considerations do not preclude performing this type of research but are a reminder to IRBs and investigators to clearly distinguish direct from indirect benefits during the consent process.

indirect benefits to subjects

Much of the genetics research to date has involved subjects affected with rare disorders caused by genetic mutations with a high level of penetrance. Research into common conditions or traits, such as adult-onset diabetes or hypertension, is likely to reveal molecular results for a gene assay that alone has weak predictive value for any given individual. Thus, although predictive risk information could be offered to subjects, it may not yet be accompanied by validated medical recommendations or prognostic information. The return of this type of ambiguous information to an individual may not be appropriate unless the potential clinical validity and utility of the findings are evaluated and integrated with other relevant data to derive a clear understanding of the uses and limitations of these data. Such follow-on questions may constitute a later phase of the study (with amendment and IRB review) or a separate protocol. If individual research results are to be returned to subjects, they must be generated in a laboratory approved under CLIA⁷ and be accompanied by the appropriate medical advice and/or counseling regarding treatment, management, and, potentially, reproductive implications.

⁶ In this example, it would be important to ensure that the consent form describes the subject's agreement to have his/her identifying information stored in a registry and his/her consent to be recontacted for future research by the original or another investigator. Furthermore, depending on the specific parameters regarding access to the information placed in such a registry, a subject's privacy authorization may be required to release his/her information to any other potential researchers. Health Insurance Portability and Accountability Act of 1996 (HIPAA), updated 2003. PL No. 104-191, Title 1, Sec. 101 and 102, 104th Congress.

⁷ See Table 24.5 for further discussion.

Table 24.3

Key Elements of the Informed Consent Process When Research Findings Will Be Made Available to Subjects

When reviewing the informed consent process for research that plans to provide subjects access to *individual* research results, IRBs should ensure that the following issues are made clear to subjects:

- What research results are likely to result from the study
- When research findings will be available
- That research goals are distinct from potential direct benefit to subjects
- Reasonably foreseeable implications of the research findings for subjects and family members
- That they may choose not to receive any individual research results or, if the study design includes the return of results, that they should consider not enrolling in the study if they do not wish to have these results returned

The IRB should further ensure that the investigator has planned for the following:

- The specific process by which research findings will be assessed for clinical use (i.e., their clinical validity and utility)
- The provision of counseling and clinical advice to inform and support subjects in the interpretation of the findings

Regardless of whether individual or aggregate research findings are to be returned, it is important for the IRB to review the proposed informed consent process to ensure that adequate information is provided. In order to minimize the risk of unrealistic expectations or inadvertent coercion, the consent process and consent document should clearly explain the research nature of the activities, the decision to return results or not, the potential implications and utility of any information disclosed to subjects and, potentially, their family members (Table 24.3), and the lack of direct benefit from participation. If it has been determined that subjects will receive individual research findings, the subjects should be given the option of not receiving them. This option may be important for subjects who are not willing to accept the potential risks related to psychological or social consequences of knowing the results, but do still wish to participate in the study. Without such an option, some may choose not to participate in the research. However, it is also reasonable for the investigator to decline enrollment of such subjects if the goals of the research depend on returning individual results and gauging the responses of the subjects to those results.

Assessing the Clinical Validity and Utility of Genetic Information Generated Through the Research

Particularly difficult challenges in determining the appropriateness of returning individual research results include the assessment of the clinical *validity* of a molecular DNA assay result and the determination of its clinical *utility* (Table 24.4). Judgment of clinical validity typically depends on studies that are repeated by multiple research groups or reproduced in different cohorts. However, in the case of novel

gene analysis, such verification may not be possible because, for example, there may not be other research groups working on the condition or the population studied may be unique. Furthermore, in the case of rare diseases, research participation may be the only access to diagnostic information or novel treatment options. Potential approaches to mitigate these issues may include:

- the review of interim findings by researchers who are not involved directly with the protocol to solicit suggestions for additional approaches to verify the findings
- awaiting scientific peer review of the relevant manuscript.

The determination of clinical utility is critical to deciding if individual results should be returned to subjects. Clinical utility can be defined as the usefulness of the findings to decisions regarding treatment, genetic counseling, or preventive strategies (SACGT 2000). For example, if results are used to identify subjects for enhanced medical surveillance (e.g., association with susceptibility for modestly increased blood pressure), it can be argued that the risks of errors in assay reliability or validity in determination of disease severity may be small and disclosure of individual research results may be justifiable. In contrast, if the findings may be used as a potential reason for subsequent prenatal testing for a genetic disease, investigators and IRBs should carefully weigh the potential implications of misinterpretation on reproductive decisions. As scientific understanding of the genetics underlying health and disease increases, it may become progressively more difficult to discern when harm to subjects might occur from not being informed about their individual research findings in order to inform personal lifestyle choices.⁸

⁸ For further reading on the concepts underlying clinical validity and utility—both clinical and “personal” utility—see *Enhancing the Oversight of Genetic Tests: Recommendations of the Secretary’s Advisory Committee on Genetic Testing* (SACGT 2000).

Table 24.4

Points to Consider Regarding the Sharing of Individual Research Findings with Subjects

General Issues

- Are the findings produced in a CLIA-approved laboratory? (See Table 24.5.)

Clinical Validity

- Are the potential findings meaningful in the clinical context?
- Have the results been confirmed in a separate study or studies?
- What is the predictive value of the assay?
- What is the estimated penetrance of the genetic trait?

Clinical Utility

- Are the findings clinically relevant to the subjects?
- Is a clinical intervention available?

As a general guide, studies that generate information that can be validated as useful to research subjects in making lifestyle or medical decisions may justify returning individual results. If information generated by the study does not meet these standards, it may be more appropriate to share aggregate results of the research with subjects, rather than individual findings (Merz et al. 2002; NBAC 2001; Reilly et al. 1997). For example, many genetic epidemiology or pharmacogenomic studies are not likely to result in investigators returning individual results, because the scientific questions posed are focused on the development of potential associations between specific genotypes and particular

traits or drug responses and are not likely to be sufficiently valid or clinically relevant to interpret at the individual level. Alternate options include specifying that in some circumstances specific results will not be returned—for example, ambiguous research information relevant to the pregnancy in studies including pregnant women, such as maternal and paternal carrier status or direct analysis of fetal cells—or that results will be returned after a particular point in time, such as after delivery in the previous example.⁹ IRBs and investigators should also note that only laboratory results generated in CLIA-approved laboratories should be returned to research subjects (see Table 24.5) (Beskow et al. 2001).

Table 24.5

CLIA and the Return of Research Findings

- The CLIA specifies that any laboratory test that is used for patient care purposes must meet certain standards.
- The standards include a laboratory certification process that is intended to assure the analytic validity of laboratory tests. It is important for the investigator and the IRB to recognize that analytic validity is the only aspect of testing that is enhanced by CLIA compliance. CLIA does not assess the diagnostic validity or the utility of such tests.
- Researchers who intend to report an individual's research results for the diagnosis, prevention, or treatment of any disease or impairment, or for the purposes of a health assessment, should have all assays performed in a CLIA-certified laboratory.
- If individual research results are to be returned to subjects (or used for clinical purposes), either the research laboratory should undergo the CLIA certification process or the findings should be reproduced in a CLIA-certified laboratory.
- IRBs should carefully review protocols to ensure that it will not be possible to readily derive results for individual subjects from the research publications if the data will not be conducted or reproduced in a CLIA-certified laboratory.

⁹ It is worth noting that pregnant women should not automatically be precluded from participating in genetics research, as there are important scientific and clinical questions to address within this population.

An additional complexity arises in returning research results to subjects in resource-poor settings, where appropriate clinical follow-up may be unavailable. Even when specific research findings are determined to be valid and useful for medical or lifestyle decisionmaking, subjects in some communities or countries may lack access to medical care or to the means to accomplish needed lifestyle changes. This issue may be particularly applicable to research conducted in developing countries (see Chapter 19 for further discussion).

Protecting the Privacy and Confidentiality of Genetic Information

Along with the realization of the potential benefits that genetics and genomics research may bring to individuals and the public generally, concerns have been expressed about who will have access to personal genetic information and how that information might be used. For example, insurers and employers may want to use genetic information as a predictor of future illness, health care costs, or the ability to perform specific job responsibilities.¹⁰ Family members, educational institutions, or the courts may also want access to genetic information to determine personal risk status, inform educational placement, or use in criminal or paternity cases. (A discussion of the requirements of the federal Privacy Rule under HIPAA¹¹ can be found in Chapter 13.) It is worth noting that “genetic information” is not distinguished from other personal and private information under the Privacy Rule. To address this issue, subjects should be made aware that, under extraordinary situations, it is possible that their genetic research data may be released to an outside party.

Under the authority of the Privacy Rule, individuals have the right to access their “protected health information.”¹² However, research data that are not used for treatment or to make clinical decisions about the individual and that are not included in a “designated record set” do not fall under the definition of “protected health information” (45 CFR Part 164.512). If research data meet these conditions, an individual does not have a legal right of access under the

Privacy Rule. In instances where the subject does have the right to access his/her individual research data, the data may be withheld until the conclusion of the full study.^{13,14}

Beyond the parameters and procedures through which an individual’s private health information can be shared within an entity or with external parties under HIPAA, the Public Health Service Act provides a mechanism, certificates of confidentiality, to protect personally identifiable research information from compelled disclosure to third parties (e.g., by subpoena).¹⁵ Because these Certificates can be obtained for research projects of a sensitive nature, including projects involving information that could reasonably lead to social discrimination or stigmatization, they may be useful to assure subjects further of the confidentiality of their participation. Certificates of confidentiality are most often used in the context of research concerning illegal behavior (e.g., illicit drug use), and it is unclear to what extent they are necessary, or effective, for enhancing confidentiality protections in most genetics research. For this reason, it is not necessary to use them routinely for genetics research, unless the genetic data are deemed especially sensitive or potentially stigmatizing or if information about illegal behavior is also being collected (NBAC 2001) (see Chapter 13 for an in-depth discussion of Certificates of Confidentiality).

Communication of a subject’s genetic research findings to family members or local health-care providers should be done with the consent and, if applicable, the HIPAA privacy authorization of the research subject. Occasionally, subjects may decide not to permit dissemination of their individual research results to the physicians who referred them to the study. If a research subject permits the dissemination of personal research findings to his/her local health-care provider, it is the responsibility of the investigator to educate the personal physician about the meaning and limitations of the findings (45 CFR Parts 164.506, 164.510, 164.522). Each of these issues should be clearly explained in the consent form and during the informed consent process. Likewise, if applicable, the HIPAA authorization statement signed by subjects prior to their participation in research should detail the disclosure policies relevant to the private health information generated or collected during the course of the research protocol according to the Privacy Rule.¹⁶

¹⁰ The use of genetic information by these parties may be limited by state laws (Hudson et al. 1995). Also see Genetic Laws and Legislative Activity, available at:<http://www.ncsl.org/programs/health/genetics/charts.htm> or Genetics and Health Insurance State Anti-Discrimination Laws, available at:<http://www.ncsl.org/programs/health/genetics/ndishlth.htm>

¹¹ See 45 CFR Parts 160 and 164 (HIPAA Privacy Rule).

¹² According to HIPAA, protected health information “[r]elates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.” See <http://aspe.hhs.gov/admsimp/pl104191.htm>.

¹³ See 45 CFR §164.524(a)(2)(iii).

¹⁴ Investigators and IRBs should also be aware of any other applicable state or federal regulations affecting the release of an individual’s personal information.

¹⁵ Public Health Service Act 42 USCA 241(d) (The Public Health Service Act §301(d), 42 USC §241(d) “Protection of Privacy of Individuals Who Are Research Subjects”).

¹⁶ See HIPAA 164.520: Notice of privacy practices for protected health information.

Children as Subjects

Samples from children may be useful for studying the inheritance of genetic mutations in families, whether or not the children are affected.¹⁷ Some research might also analyze DNA from asymptomatic children for adult-onset disease traits, disease susceptibilities, and carrier status. Such testing raises ethical and legal issues that focus on the interests of children and their parents (Nelson et al. 2001), and the issues will vary depending on whether the research study includes the return of individual research findings. Currently, there are no formal professional guidelines regarding genetic testing in children for research purposes; however, recommendations regarding pediatric genetic testing for clinical purposes (i.e., disease testing) may be helpful. A 1995 joint statement by the American Society of Human Genetics and the American College of Medical Genetics declares that the primary goal of *clinical* genetic testing should be to promote the well-being of the child (ASHG/ACMG 1995). In addition, because children grow through stages of cognitive and moral development, professionals should be attentive to the child's changing abilities and interest in participating in research studies. (See Chapter 21 for a discussion of the involvement of children in research.)

There are several points to consider when assessing the risks and potential benefits posed by genetic research findings in children. If there is no prospect for direct benefit and research results will not be returned, children may be included in the study if the criteria are met for research involving no more than minimal risk without direct benefit

(see Chapter 21).¹⁸ This may often be the case, as the primary risks of physical harm associated with genetic assays are frequently those surrounding phlebotomy or buccal swab collection. If, however, there is a prospect of direct medical benefit from a genetic assay (e.g., when the disorder manifests in childhood) and direct medical benefits may be possible, the research may be allowable with children even if the risks are greater than minimal¹⁹ (see Table 24.6).

Research that includes genetic analysis for heritable disorders in at-risk unaffected children can include risk for adverse psychosocial consequences (ASHG/ACMG 1995; Suter 1993). One potential motivation for participation that should be considered when reviewing this type of analysis is that parents may harbor guilt for possibly transmitting mutant alleles to children who would be carriers for or at risk for developing a disease. Controversy surrounds the issue of testing children for their genetic status for a heritable disorder (with return of individual research findings) for the principal purpose of alleviating parental anxiety or guilt. Some suggest that this type of analysis is rarely appropriate for children (ASHG/ACMG 1995), and others state that it should be the parents' decision (Michie et al. 2001). Furthermore, the testing of older children with the return of individual results raises difficult questions surrounding the autonomy of adolescents and emancipated minors and other complex issues. Testing children and returning individual findings for adult-onset lethal conditions (e.g., Huntington's disease) for which there are no treatments is particularly problematic, as the risks are believed to most often be greater than any potential benefits (ASHG/ACMG

Table 24.6 Potential Clinical Uses for Genetic Research Findings in Children

Medical issues that research findings may elucidate:

- *Treatment and prevention*—For example, a child with familial high cholesterol may benefit from dietary management.
- *Surveillance*—For example, in retinoblastoma, monitoring can lead to effective treatment (Gallie et al. 1991).
- *Reduction of surveillance*—For example, a child with a family history of Von Hippel-Lindau disease may avoid further surveillance procedures when test results are normal (Glenn et al. 1992).
- *Refinement of prognosis*—For example, specific genotypes related to cystic fibrosis may predict the risk of developing pancreatic insufficiency (Estivill 1996; Freedman 2002; Reboul et al. 2002; Zielenski 2000).
- *Clarification of diagnosis*—Genetic testing may provide clarification of an uncertain diagnosis if diagnostic data from other sources are inconclusive. For example, it may confirm a diagnosis of neurofibromatosis in an individual whose physical exam is inconclusive.
- *Assessing familial recurrence risks*—In unusual circumstances, testing of a child for a heritable disorder may determine the parents' risk of having a subsequently affected child.

¹⁷ For the purposes of the discussion within this section, *children* refers exclusively to minor individuals and not to the adult children within a given family.

¹⁸ See 45 CFR 46.406.

¹⁹ See 45 CFR 46.405.

investigators should demonstrate the benefits of testing children

1995; Beauchamp and Childress 2001; Nelson et al. 2001).

However, these concerns have not been thoroughly studied within the broad population. In

order to empirically assess the benefits and potential risks of harm to children and their parents in such complex health situations, it may be scientifically and ethically valid to pursue research specifically focused on questions surrounding the return of genetic research results to children and adolescents. In all cases, investigators should demonstrate that the benefits of testing children and returning research findings to them (or to their parents) outweigh the risks of harm.

C. Research Involving Families

By their nature, genetic assessments directly or indirectly include information about the relatives of the person being studied. It is important to distinguish between the clinical and research contexts for including such information in an analysis. In many cases, family information is needed to diagnose an individual as part of a diagnostic and therapeutic assessment, not as part of a research study. Thus, it is important to recognize the difference between collecting this information in order to confirm a diagnosis in an individual seeking clinical care and collecting this information for the purposes of research.

In the context of research, it is possible that participation in some genetics studies may alter (positively or negatively) family relationships (ASHG/ACMG 1995; Beeson and Doksum 1999; Botkin 2001; Fanos and Johnson 1995; Hoskins et al. 1995; Patenaude 1998). Even the solicitation of research participation within extended families may expose differences among relatives in attitudes or beliefs, which may cause problems in the family. When individual research findings are returned to subjects, there is a potential to differentiate, or sort, relatives based on their “at-risk” status, disease status, or reproductive risks, and this can potentially create undesirable changes in family dynamics. Furthermore, genetics research may raise issues stemming from the discovery of misidentified relationships, such as misattributed paternity or unknown adoption. These types of risks may also affect family members who are not participating in the research. Therefore, IRBs should consider how to handle situations in which close family members (e.g., parents of adult children or identical twins) choose not to participate in the research. IRBs should ensure that any reasonably foreseeable psychological or social harm to which the research subject may be exposed is explained during the consent process (National Commission 1979; WMA 2002). Further exploration of these issues can be found in *Assessing Genetic Risks* (IOM 1994)

and other publications (Beauchamp and Childress 2001; Brody 2002; Knowles 2002; Lucassen and Parker 2001).

Are Family Members Research Subjects?

To generate data relevant to a specific genetics research question, it may be necessary to collect a pedigree that includes information about (unenrolled) relatives of an enrolled subject. Pedigree information typically includes age, gender, health information, and the relationship (e.g., sister, nephew) of each person to the subject (in the context of pedigree research the original subject is referred to as the “proband”). The analysis of pedigree information is often critical to determine a potential mode of inheritance, penetrance, expressivity, and the range and severity of a disorder for the proband. (As noted above, this analysis might also be conducted in the context of clinical care.) In addition, some studies require pedigree information to map and identify genes. The unenrolled individuals about whom such information is collected to generate the pedigree are often referred to as “third parties.”

analysis of pedigree information

Depending on the nature of the information collected, third-party individuals may be affected by the research. An important issue for investigators and IRBs is determining when the information that is collected requires that a third party be classified as a human research subject in accordance with §____.102(f). This currently is a controversial and unsettled area of human subjects protection for genetics research. Until clear guidance is available, investigators and IRBs should use their best judgment in determining when information on such third parties is both identifiable and private, when third parties must be consented, and when a waiver of consent for a third party would be appropriate.

When applicable, the protocol should also include a description of the procedures for the contact and enrollment of the third parties as research subjects. Some types of information collection can simply be described in the protocol (e.g., if the third party is deceased or if the information will not be both individually identifiable and private). In all cases, appropriate confidentiality protections should be put in place for any information collected, and these protections should be outlined in the protocol.

Contacting and Enrolling Subjects in Family Studies

Because of the significant proportion of genetics research involving family studies or the study of rare diseases, it is particularly important for investigators and

IRBs to prospectively consider the most effective and ethical recruitment strategies to successfully implement a protocol (see Table 24.7). There are multiple approaches to the initial contact of potential subjects for a research study. In most instances, contact with the potential subject to introduce the project is initiated through a proxy, such as a letter, e-mail, phone call, or contact from a relative or acquaintance who is already enrolled in the study. The design of this approach can be in the form of opting-in or opting-out (Rogers et al. 1998):

- Under the opt-in mechanism, the potential subject must actively contact the investigator/research team to initiate a discussion about potential participation in a study. For example, the investigator may mail a letter of invitation to a relative of the proband in a

particular study,²⁰ or relatives may be given verbal information by the proband directly. This option maximizes the autonomy of individuals but may reduce recruitment levels.

- In the opt-out case, a letter, postcard, or phone call, for example, informs potential subjects that they must actively decline to be contacted by the research team by a particular date. Under this model, the investigator may contact family members, or other identified individuals who have not responded to the initial information, once the specified period of time has elapsed.²¹ Although this strategy may lead to higher recruitment levels, it may excessively compromise autonomy.

Table 24.7
Advantages and Disadvantages of Various Contacts to Initiate Discussion of Potential Research Participation

	Advantages	Disadvantages
Family Member (Proband)	<p>May be on familiar terms with other family members.</p> <p>May be viewed as minimally intrusive by other family members.</p> <p>May be highly motivated.</p>	<p>May know potentially embarrassing private information.</p> <p>May pressure family members to participate.</p>
Family Physician	<p>May be on familiar terms with family.</p> <p>May be a trusted contact for the potential subject and family. May be motivated to improve care via research.</p>	<p>May know potentially embarrassing medical information.</p> <p>The potential subject may perceive pressure to participate, believing that research participation is necessary to maintain physician's approval.</p>
Investigator	<p>May be most knowledgeable on study.</p> <p>Subjects may be most comfortable refusing this person.</p> <p>Highly motivated to recruit.</p>	<p>May not be best to provide information in a personal context.</p> <p>May present overly optimistic picture of potential benefits.</p> <p>May know little about any relevant family issues.</p>

²⁰ If applicable, appropriate authorization must be obtained to reveal the private health information of the proband according to the provisions within the Privacy Rule (Kokkedee 1992).

²¹ Ibid.

Investigators and IRBs should consider the relative advantages and disadvantages of the methods that might be used to establish initial contact with potential subjects (see Table 24.7). For example, would it be most appropriate for contact to originate from an enrolled subject (typically a family member in genetics studies), a referring clinician, the principal investigator, or another member of the research team? It is important that the investigator, in consultation with the IRB, make a determination on this point that minimizes potential harms, such as coercion, misinformation, and any disruption of family relationships, while supporting recruitment and the potential benefits of participation.

Researchers who study rare diseases must overcome the dual challenge of identifying individuals with the condition and the likely need to recruit family members. To attract potential research subjects, these investigators may need to make their research interests known to the medical community and, increasingly, to the patient advocacy community. This particular route is largely a passive process in which the investigator receives referrals from physicians or members of advocacy groups who know about the investigator's research interest.

Groups of individuals, particularly population isolates in which social or geographic isolation may have led to fairly common expression of unique attributes, are also of particular interest to geneticists because of the special opportunity they present for linking a specific inheritance pattern to a clinical manifestation. In some of these special situations, studies may be designed for direct, initial contact by a researcher (Gross et al. 2002; Weijer 1996). The researcher may learn of the potential subject through a family member and directly telephone or write to the person, introducing themselves and the research study. An example of such a study would include some field research studies of sociocultural isolates (for example, the Old Order Amish or Hutterites). The IRB should ensure that the informed consent process in these instances reflects reasonable planning regarding the nature of this initial conversation and the nature of the information that is to be discussed prior to obtaining consent to enroll in the study (Annas 2001; NBAC 2001).

Publication of Pedigrees

In the scientific publication of studies involving rare genetic disorders or large, unique families, illustration of important pedigree information without enabling identification of an individual or family can be challenging. In these situations, IRBs should keep in mind that every individual within a family deserves to have his/her personal

information kept confidential. Family members are not entitled to each other's genetic information or diagnoses (or information pertaining to familial relationships). Therefore, before revealing medical or personal information about an individual to other family members, it is important that investigators obtain the express consent of that individual to do so.

When pedigree data are necessary to communicate research results in a publication, the potential risks should be discussed with research subjects during the informed consent process. This discussion should include issues regarding privacy and confidentiality to individual, family, and, in some cases, unenrolled third parties. According to the recommendations of the International Committee of Medical Journal Editors (ICMJE), research subjects should be asked to consent to the inclusion of their information in pedigree data after an opportunity to review the completed manuscript.²² Others have argued that such an act still exposes individual subjects to intrafamilial risks of disclosure (Botkin et al. 1998; Frankel and Teich 1993). Another mechanism to minimize such risks is obtaining, prior to publication, the prospective consent of subjects to publish their information among the pedigree data (Botkin et al. 1998); however, this would conflict with the ICMJE policy.

Because of these complexities, both investigators and IRBs should prospectively consider the need for pedigree dissemination when deciding if individual research results will be shared with subjects (see discussion above). If the individual results for particular research subjects can be determined from a published pedigree, it may appear disingenuous to design the study as one that does not return individual research results. Some have advocated that pedigrees should be masked or altered to avoid the identification of individual subjects; however, this is controversial because important scientific data may be lost or misinterpreted by readers (Privacy Matters 1998). In no case should this be done without the agreement of the journal editor and proper disclosure in the paper. The consent process should disclose that, although individuals will not be explicitly identified in the pedigree data, their identity might be obvious to those familiar with the family or the individual.

D. Research Involving Specific Populations or Communities

While most genetics protocols are open to research subjects from any ethnic group or geographic origin, the targeted recruitment of subgroups may be scientifically appropriate. The justification for targeted recruitment is

²² See www.icmje.org.

based on the fact that some disorders are more common among individuals affiliated with specific ethnic, geographic, or religious groups and the study of subjects from such groups can facilitate association or linkage studies and gene

population isolates

identification. The genetic similarity and ancestral commonality of population isolates may also facilitate the study of common diseases, as well as rare conditions. However, due to the diversity of sensitivities regarding genetic information and the variety of cultural interpretations of genetic variations, the need to consider the potential effect of proposed research on identifiable groups or populations is especially important in genetics studies (Beskow et al. 2001). For these reasons, when a subpopulation is being studied to derive information useful to a wider population, investigators and IRBs should be particularly attentive to considerations of justice and beneficence (e.g., that the subpopulation should benefit from the study at least as much as does the wider population).

Whenever a readily identifiable group is studied, there is a potential for “group stigmatization,” particularly if the group is to be identified in the dissemination of the research findings (Juengst 1998; Wilson and Junger 1968). For example, members of the Jewish community have written about the potential for stigmatization resulting from the identification of “Jewish genes,” which could fuel a perception of genetic inferiority of their population (Reilly 1998; Stolberg 1998). It is important that IRBs examine the inclusion criteria within any given study to determine if an identifiable group or population is being sought. If so, IRBs should assess if the targeted recruitment is scientifically and ethically justifiable and there are mechanisms in place to minimize group harm posed by the study. In reviewing such protocols, the IRB should ensure that the interests of the targeted population are protected in accordance with the level of risk presented. However, this group protection should not compromise the autonomy of individuals within the group (see below).

The IRB may advise investigators to actively engage members of the targeted population in the research development process to ensure that the research goals and outcomes are clear, understandable, and appropriate within the context of the specified population (Juengst 1998). The IRB may also want to consider whether the investigator has established a relationship with the group (e.g., through prior research interactions), engaged coinvestigators with expertise in the sociology of a particular group, or sought advice from the group that would be able to alert them to concerns that might arise in the course of the research. Alternatively, the IRB may choose to engage a representative of, or an expert on, the group as an ad hoc IRB member for the review of that protocol (Foster et al. 1998).

When relevant, community consultation is advised in addition to, but not in place of, individual informed consent processes, it is important to emphasize that the primary purposes of group or community consultation is to inform investigators of the needs and interests of the group and to promote understanding of the research by the community in order to avert avoidable errors or harms prior to commencing the research. It has been argued that a community or group decision against a research study subverts the autonomy of individual members of that group who may wish to participate (Beskow et al. 2001; CDC 1998; Foster et al. 1998; Gostin 1991; Juengst 1998). Because respect for individual autonomy is one of the three pillars of U.S. research ethics, this consideration cannot be ignored. When considering research conducted internationally, this point may be confounded by national laws, local cultural views, and varying approaches to research and informed consent (see Chapter 19 for further discussion of informed consent in international research). Furthermore, the increasing presence of non-Western cultures within the United States may progressively challenge the social assumptions underlying the U.S. regulations on informed consent practices (Angell 1997; Christakis 1992; Love and Fost 1997; Pellegrino 1992).

Increasingly, research ethics has had to grapple with the potential tension between community interests or norms versus individual choices or interests. It is helpful to recognize that the definition of community can itself be complex (Weijer and Emanuel 2000) and that individuals have coexisting membership in multiple communities defined in different ways. There is no accepted standard practice for determining who can speak for a community or how community representatives can be selected for the purpose of soliciting views on research, whether it is genetics research or any other kind. As mentioned above, researchers’ knowledge and experience regarding the community in question, and relevant social science expertise, may help in assessment of the appropriateness and acceptability of the research. However, even given these efforts, uniformity of opinions is unlikely in any setting, and tension between or among community members with differing views on research may occur. Researchers cannot resolve these tensions, but they can approach the issues thoughtfully and respectfully to try to reach workable agreements.

E. Genetics Research with Stored Samples or Information

Although the general issues of research on stored human biological specimens are covered in Chapter 18, there are some issues that are particularly relevant to

genetics research that deserve further attention here. With the human genome sequence essentially complete and the mounting knowledge of specific sequence variation patterns (such as single nucleotide polymorphisms [SNPs] and haplotype maps), researchers will continue to identify and link particular gene sequences to observable phenotypes or clinical outcomes. Studies to pursue such genetic links may involve requests to use previously collected samples for new research purposes. Use of these samples obliges researchers and IRBs to consider the rights and welfare of the individuals who provided them, especially when samples retain identifiers.

As discussed in Chapter 18, samples stored within a repository or information contained within a databank should be used in accordance with the IRB-approved protocol. If informed consent is required, the consent document should clearly state what uses are permitted and these uses should be explicitly discussed during the informed consent process. The investigator should clearly specify his or her plan for long-term storage and any foreseen current or future use. If future research use is planned, the proposed duration of the storage and the potential uses of the sample (e.g., commercialization or sharing with other investigators) should be discussed during the consent process (Clayton et al. 1995).

Researchers may offer the option of participating in their proposed research project without long-term sample storage and future use; however, they should have adequate resources to accommodate the substantial challenges involved with tracking the use of individual samples within the laboratory. If such an option is offered to subjects, consent forms may require more than one signature, one for participation in the proposed research and one for sample storage for future research purposes. In some cases, it may not be practicable to track samples for future use/nonuse (e.g., in very large studies), and the researcher should be explicit that the subject should enroll in the study only if he or she is comfortable with the study's short- and long-term research goals. In either case, withdrawal of the specimen in the future should be permitted if possible (see discussion below).

Identifiability of Stored Samples

Generally speaking, investigators must explain to a potential research subject that he or she may withdraw from study participation at any time.²³ Investigators who retain genetic information in databases or sample collections should specify what would happen, upon withdrawal, to any individual research results or private health information

collected during the study. Investigators also should not state that complete withdrawal is possible, if it will become impossible at some point in the future. This aspect of the informed consent discussion is particularly important in some types of genetics studies such as, for example, when a subject agrees to donate a DNA sample to a research repository in which the sample will be de-identified and subsequently distributed to researchers around the world. In these situations, there will likely be a point after which the sample, or the results obtained from the sample, cannot be withdrawn from the databank or repository. Likewise, if sequence or other data were published, it may be impossible to withdraw the information from the public domain. The parameters of any such limitations should be disclosed and explained in the course of the informed consent process and documented in the consent form. Similar caveats and limitations should be explained to subjects within the authorization statement permitting the disclosure of private health information. Specifically, the time period during which information will be used or disclosed must be defined, and any allowable limitations on the revocation of authorization must be detailed²⁴ (for further discussion see Chapters 13 and 18).

Proposed Use of Stored Material

The issue of secondary use of samples or data is particularly challenging when samples from one research study become useful for another study that may not have been envisioned at the time of the initial informed consent process. This will continue to be a challenge to genetics research as the understanding and knowledge of the human genome sequence evolves. One view is that, even when the new research topic is seemingly unrelated to the prior study, if the nature of the risks and benefits of the original and the proposed study are comparable, it may be possible for the samples to be used (ACMG 1996; ASHG 1996; Clayton et al. 1995; NBAC 1999). For example, an IRB might permit samples from a study of cardiac muscle genes in hypertension to be used for a study of kidney salt transport molecules in hypertension, because it is difficult to imagine that a research subject would be harmed by this new usage as the associated risks to participation are similar, and they were originally participating in a study to understand hypertension. However, the use of samples from a hyperlipidemia study for a study of early onset dementia could be problematic, because the potential psychosocial harms of these two pursuits differ substantially, and it is easy to imagine that there may be subjects who would be willing to participate in one but not the other. In such instances, the IRB should assess whether the proposed secondary use of

²³ See 45 CFR 46.116.

²⁴ National Center for Human Genome Research-Department of Energy Guidance on Human Subjects Issues in Large-Scale DNA Sequencing, issued August 19, 1996. Available at www.ornl.gov/TechResources/Human_Genome/archive/articles/nchgrdoe.html.

Secondary use of stored material

the sample or associated information requires specific consent by selected subjects or whether a waiver of consent is justifiable. Likewise, the responsible privacy entity for the research organization (e.g., Privacy Board or IRB) should determine whether a new authorization to disclose the private health information is necessary or whether a waiver for this requirement can be issued.

It may be possible to substantially ameliorate the risks of secondary uses of specimens by de-identifying them. However, this may not always be feasible or desirable for certain types of research (e.g., longitudinal studies) where a link to the subject must be retained (see Chapter 18 for further discussion).

Research Use of Samples or Information from Deceased Individuals

Although deceased individuals are not considered research subjects according to the Common Rule,²⁵ the IRB

may wish to consider the degree to which it may be possible for research on a sample collected from a deceased individual to have direct implications or consequences for living relatives (DeRenzo et al. 1997). Although it is not likely to be necessary to obtain the consent of living relatives for such research, in unusual cases such as research with samples from deceased newborns, it may be appropriate to consider options to minimize potential harms to living individuals. Discretion in the presentation of any data or individual research results is a primary mechanism to limit exposure to risks of harm for family members. However, in those unusual cases where IRBs and investigators determine that further protections are appropriate and reasonably practicable, relatives could be engaged in a discussion of the research and the potential psychosocial risks to family members. The depth of any such discussion should be calibrated to the specific risks and benefits presented for the family members within a given study. It may be helpful for IRBs to evaluate the potential effects of this type of proposed research on living relatives using similar parameters to those used in research within identifiable groups or specific communities.

²⁵ See 45 CFR 46.102(f).

Key Concepts: Questions in Genetic Research

Research with Individuals

- Are subjects adequately informed about the risks and benefits of the research and of any potential genetic information generated to themselves or their families?
- Under what circumstances, if any, will individual research results be provided to subjects or their physicians?
- To what degree will the research subject directly benefit or be exposed to risk of harm from receiving individual research findings?
- What is the clinical validity and utility of genetic information generated through the research?
- Are appropriate privacy and confidentiality protections in place?
- Will children be among the potential subject population for a study that includes genetic analysis? If so, how will the child's well-being be protected?

Research Involving Families

- Does the information collected about family members of the subject require them to be enrolled as research subjects?
- How will potential subjects be contacted and recruited for study participation?
- Will pedigree data generated through the research be published?

Research Involving Specific Populations or Communities

- Will genetic data generated through the study of a specific population be linked to the group either explicitly or implicitly?

Genetics Research with Stored Samples or Information

- Will donated samples or genetic information remain identifiable or linked in any way to subjects upon their withdrawal?
- Is the proposed use of stored material based upon emerging genetic knowledge that was not available at the time of sample collection?
- Are the risks and benefits of the proposed research study comparable to that of the original study?
- What are the potential risks and benefits, if any, of research using samples or information from a deceased individual for living family members?

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Appendix 24.A: Glossary

Allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type.

Association: The presence of an allele in increased or decreased frequency in affected subjects compared with control subjects.

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Genome: All of the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria.

Genotype: The genetic identity of an individual that does not show as outward characteristics.

Haplotype: The specific pattern of alleles along an individual chromosome. Studies have shown that chromosome haplotypes are composed of blocks that have only a few common haplotype patterns. The allele patterns of these blocks can identify or “tag” the distinct haplotype.

Linkage: The tendency of genes and/or specific sequence variations that lie near each other on a chromosome to be inherited together.

Penetrance: The likelihood that a person carrying a particular mutant gene will have an altered phenotype.

Pharmacogenetics: The study of genetic variations that influence responsiveness to pharmacologic therapies. The responsiveness may include measures of efficacy as well as measures of toxicity or side effects.

Phenotype: The observable traits or characteristics of an organism (for example, hair color, weight, or the presence or absence of a disease). Phenotypic traits are not necessarily genetic.

Proband: The first identified affected individual in a family.

SNPs: An abbreviation for “single nucleotide polymorphisms” (commonly pronounced as “snips”). SNPs are individual nucleotide differences that occur in human DNA at an average frequency of one every 1,000 bases. SNPs are one type of genetic marker (see above).

Chapter 25

Gene Therapy/Human Gene Transfer Research

- A. Human Gene Transfer Research (“Gene Therapy”)
- B. A Brief History of Human Gene Transfer Research
- C. Special Federal and Local Oversight Framework
- D. Special Safety and Human Subjects Protection Considerations
- E. Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Research Subject

Key Concepts

References

Appendix 25.A: Excerpts from Appendix M of the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules



A. Human Gene Transfer Research (“Gene Therapy”)

Human gene transfer, often called *gene therapy*, refers to the process of transferring specially engineered genetic material (recombinant DNA or RNA derived from recombinant DNA) into a person. Human gene transfer is being studied to see whether it could treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease. Currently, human gene transfer is experimental and has not been approved in the United States for clinical use in treating any condition. To avoid the misconception that this technology is therapeutic, the term *human gene transfer research* is preferred to *gene therapy*.

Currently, human gene transfer is targeted to somatic, or nonreproductive, cells so that the insertion of genetic material is intended to affect only the individual who has received it. Theoretically, human gene transfer research also could be directed toward germ, or reproductive, cells with the aim of changing the set of genes passed on to the individual's offspring. However, because of technical challenges, safety issues, and, as important, ethical concerns, it is not yet feasible or desirable to transfer genes into human reproductive or germ cells. For example, human gene transfer has the risk of *unintentional* germ-line gene transfer, and a gene transfer vector has been found in the semen of at least one gene transfer subject. At this time, no federal

agency will fund or review research involving intentional germ-line gene transfer.

B. A Brief History of Human Gene Transfer Research

Early references to a scientific approach to carrying out human gene transfer appeared in the literature in the 1960s, a time when the nature and structure of DNA had been only recently elucidated and it seemed possible for the first time that scientists might be capable of genetically modifying life forms. In the 1970s, recombinant DNA techniques were developed, and genetic engineering of life forms became a reality. After gene transfer was first successfully conducted in microorganisms, it took little imagination to realize that this technology might soon be applied in higher-level organisms, including humans.

An early landmark event in the development of the current U.S. system of oversight was the Asilomar Conference of 1975, which assessed the biohazard issues associated with recombinant DNA research. As a result of the conference, the National Institutes of Health (NIH) was identified as a key locus for federal oversight of the scientific, safety, and ethical issues associated with this technology. At the end of this event, the Recombinant DNA Advisory Committee (RAC) was first convened to advise NIH

**Recombinant DNA
Advisory
Committee (RAC)**

on how to address the potential risks associated with recombinant DNA research. In 1976, the first official NIH guidelines for conducting recombinant DNA research were published as an outcome of a public process by which scientists developed safety standards for the containment of recombinant DNA research.

In 1990, the first human gene transfer research protocol was initiated. A four-year-old girl with adenosine deaminase (ADA) deficiency received an infusion of autologous T cells into which a normal ADA gene had been inserted. The procedure took place in the Pediatric Intensive Care Unit of the NIH Clinical Center.

Since that time, hundreds of trials have been undertaken, and the scope of targeted diseases and conditions has expanded greatly. Today, the majority of human gene transfer studies target various types of cancer. Other human gene transfer trials are directed at monogenic diseases such as hemophilia or cystic fibrosis, infectious diseases such as AIDS, vascular conditions such as coronary artery disease, and a host of other disease indications. Human gene transfer studies are still largely in the early phases, where only the safety of the intervention is being tested; no gene transfer products for the cure of any condition or disease are yet available in this country.

C. Special Federal and Local Oversight Framework

Two agencies, the Food and Drug Administration (FDA) and NIH, provide special oversight of human gene transfer research at the federal level. Locally, human gene transfer research is reviewed by Institutional Biosafety Committees (IBCs) in addition to Institutional Review Boards (IRBs). Special review and safety reporting requirements highlight the importance of communication and information sharing among these bodies. These mechanisms are described below.

The Role of FDA in Human Gene Transfer Research

FDA's role is to determine whether or not a sponsor may begin studying a gene transfer product and, ultimately, whether it is safe and effective for human use. This process of review and authorization of gene transfer research is conducted by FDA's Center for Biologics Evaluation and Research (CBER). Sponsors of gene transfer products must test their products extensively and meet FDA requirements for safety, purity, and potency before they can be administered to humans or sold in the

**Center for Biologics
Evaluation and
Research (CBER)**

United States. FDA regulates the products evaluated in human gene transfer clinical trials that are intended for eventual sale in the United States and is responsible for reviewing serious adverse events that occur in a gene transfer study. The agency consults with and receives advice from its Biological Response Modifiers Advisory Committee on scientific issues related to gene transfer products.

A manufacturer who is considering selling a gene transfer product in the United States first must tell FDA of its intentions and then must test the product in a laboratory and then in research animals. When a manufacturer is ready to study the gene transfer product in humans, it must obtain an Investigational New Drug (IND) Application. In the IND application, the manufacturer explains how it intends to conduct the study, what possible risks may be involved, and what steps it will take to protect patients, and it provides data in support of the study (21 CFR 312.23). The study then must be reviewed and approved by an IRB, which focuses on protecting persons who may participate in the study. Researchers also must obtain and document the legally effective informed consent of the prospective subjects (see Chapter 12 for information about informed consent requirements).

When FDA's scientists receive an IND application for gene transfer, they review it before permitting the manufacturer or researcher to begin the study. FDA may ask the study sponsor to do more laboratory tests and include more safeguards to ensure the safety of patients, such as giving patients smaller doses. If unexpected problems arise, FDA may tell the manufacturer to change the study or stop it altogether.¹

The Role of NIH in Human Gene Transfer Research

NIH is the major public funding agency for biomedical research, supporting, among many other lines of scientific investigation, much laboratory and clinical research on vectors, disease models, and the human applications of gene transfer technologies. In carrying out this function, the agency assumes stewardship and oversight responsibilities for promoting the safe and responsible conduct of this research. With respect to human gene transfer research, NIH's primary role is to evaluate its scientific, safety, and ethical aspects and communicate its findings to the scientific community, IRBs and IBCs, and the public.

The *NIH Guidelines for Research Involving Recombinant DNA Molecules* (NIH 2002) articulates standards for investigators and institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived from recombinant DNA. This document outlines the

¹ For more information regarding FDA's role in human gene transfer research, see www.fda.gov/cber/infosheets/genezn.htm.

Guidelines for Research Involving Recombinant DNA Molecules

requirements for institutional oversight. Appendix M of the guidelines describes points to consider in the design and submission of human gene transfer trials, including the

registration of protocols with NIH, the review procedures of the RAC, the conduct of informed consent, and annual and expedited reporting requirements. Institutions that receive NIH funding for basic and clinical recombinant DNA research must ensure that all research conducted at or sponsored by the institution complies with the *NIH Guidelines*.

NIH oversees human gene transfer research through its Office of Biotechnology Activities (OBA), which manages the RAC. NIH convenes the RAC to conduct in-depth review and public discussion of the scientific, safety, and ethical issues associated with selected gene transfer protocols. The RAC review process also focuses on emerging policy issues in recombinant DNA research. All human gene transfer protocols occurring at or sponsored by institutions receiving NIH funds for recombinant DNA research must be submitted to the NIH OBA for review by the RAC. In addition, investigators must follow certain scientific and ethical principles and comply with safety reporting requirements.

The Role of IBCs

An IBC is a review body responsible for ensuring that basic and clinical recombinant DNA research is conducted safely and in accordance with the *NIH Guidelines*. IBCs were established under the *NIH Guidelines* to provide local, institutional oversight of nearly all forms of research utilizing recombinant DNA. However, institutions often assign the IBC additional responsibilities for the review and oversight of a variety of experimentation that potentially involves biological hazards, such as infectious agents and carcinogens. The IBC must review and approve all experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into any human research participants. Although IBCs are concerned about the safety of human subjects, they are primarily charged with broader safety concerns involved in recombinant DNA research—for example, unintentional release of genetically modified organisms, safety for laboratory personnel, and community well-being. IBCs and IRBs both have responsibility in the oversight of human gene transfer research and should communicate on matters of common concern.

Availability of RAC Recommendations to IRBs and IBCs

The RAC review process can inform the discussions that IRBs and IBCs will undertake as part of local review of human subjects research studies. The RAC review process

can result in recommendations on scientific (e.g., study design) and ethical (e.g., the adequacy of informed consent) matters, which are provided to the Principal Investigator (PI) following the RAC meeting in a letter prepared by OBA staff. This summary letter is also sent to the IRB and IBC reviewing the protocol, FDA, and the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). IRBs and FDA may review protocols before or after RAC review, but will nonetheless be notified of the RAC recommendations. Final IBC approval of human gene transfer studies subject to the *NIH Guidelines* may not occur until after the RAC review process has been completed.

National Level Analysis of Safety Data

Investigators have an ongoing responsibility to monitor human gene transfer trials and to keep OBA, as well as IRBs, IBCs, FDA, and any sponsoring NIH institutes or centers, informed of any adverse events that occur in a trial. If a serious adverse event occurs that is unexpected and could be possibly associated with the gene transfer product, a sponsor is required by regulation to notify FDA within 15 days of the event, and investigators should notify OBA of the problem within 15 days of their notification to the sponsor. Serious adverse events that are fatal or life threatening must be reported within seven days. If warranted by the nature of these events, FDA may mandate changes to the human study, require more preclinical studies, put the clinical study on hold, or stop the study altogether.

NIH and FDA have developed a national database for gene transfer clinical research, the Genetic Modification Clinical Research Information System (GeMCRIS) to enable systematic analysis of data across all human gene transfer trials and to enhance communication and application of knowledge gained from the studies. The system provides a standardized means for reporting, organizing, and analyzing data related to adverse events in a format accepted by both NIH and FDA.

D. Special Safety and Human Subjects Protection Considerations

Risks of Gene Transfer

The risks of gene transfer can vary based on the nature of the disease indication, the phase of the clinical trial, and the gene delivery method used. In human gene transfer, genes are inserted into the body through vectors. Currently, the most common vectors are viruses, such as retroviruses and adenoviruses. Viruses, while effective, can cause clinically significant problems, such as inflammatory re-

sponses and gene control and targeting issues. Alternative vector systems are being investigated, including complexes of DNA with lipids and proteins.

Potential risks of gene transfer studies include those associated with the study procedures as well as risks of harm associated with the study agent. For example, the added vector or gene could:

- disrupt properly functioning genes in the cell and predispose the cell to cancer or other abnormalities (insertional mutagenesis);
- reach other untargeted cells or tissues in the body;
- become replication competent and be passed on to close contacts through infection;
- trigger a severe immune system response; or
- be inadvertently introduced into germline cells, creating permanent cellular changes that could be passed on to future generations.

In some cases, the potential risks associated with gene transfer may weigh against the involvement of human subjects in such trials. IRBs need to consider the risks and benefits of a human gene transfer study carefully and, if a protocol is approved, ensure that participants will be thoroughly informed of the risks and benefits involved in the procedure.

Subject Selection

According to the *NIH Guidelines*, human gene transfer protocols that are submitted to the RAC for review should describe methods for subject selection, including the numbers of subjects, the recruitment procedures that will be used, the exclusion and inclusion eligibility criteria that will be applied, and how the investigator will select among eligible prospective subjects if it is not possible to include all who desire to participate.

The involvement of healthy volunteers has to be considered carefully in any clinical research study, including gene transfer research. In general, healthy volunteers have no prospect of any direct benefit from participation in research, yet they subject themselves to risk. Consequently, most studies involving healthy volunteers typically are of relatively low risk to be ethically justifiable. To date, few human gene transfer studies are considered to be of low risk; thus, few of these studies involve healthy volunteers as subjects. Those that do are generally phase 2 safety studies, in which the involvement of healthy volunteers is necessary to avoid the presence of factors, such as illness, that may mask or confound the observation of possible toxicities.

Informed Consent

Extra care must be taken during the informed consent process to communicate to the prospective research subject the special issues raised by gene transfer, such as horizontal and vertical transmission of gene products and their vectors, in language that is understandable to the subjects. Specifically, IRBs should consider how the innovative character and the possible (known and theoretical) adverse effects of the study will be discussed with subjects, how the potential adverse effects will be compared with the consequences of the disease, and what will be said to convey that some of these adverse effects, if they occur, could be irreversible. In addition, because of the problem of therapeutic misconception, investigators should avoid unrealistically raising the hopes of the subjects and their families. For example, the informed consent form should not describe the experimental intervention as “therapy” or “treatment.” OBA has developed an online guidance for informed consent in gene transfer research.²

Gene Marking Studies

Gene marking studies are early phase studies designed to track the movements of cells and genetic material that have been introduced into subjects to better understand the mechanism by which a possible gene transfer approach might be used to treat disease. Marking studies generally are not designed to test the therapeutic value of a gene transfer product.

Those who participate in gene marking studies should be informed that the studies are designed to advance general knowledge, that subjects are highly unlikely to benefit from them, and that these studies may be of benefit to future patients by helping to advance scientific and medical knowledge. Therefore, approval of gene marking study protocols should hinge on data demonstrating that the specific intervention planned is safe and is highly likely to yield knowledge of value. In addition, the investigator also should provide evidence that such knowledge could not be obtained by non-gene transfer approaches or animal gene transfer experiments. Gene marking studies are considered undesirable when the intervention is especially risky.

Long-Term Follow-up and Patient Monitoring

Because gene transfer is innovative and its long-term risks are not well understood, the *NIH Guidelines* require investigators to inform prospective participants that they will be asked to participate in long-term follow-up that extends beyond the active phase of the study. Investigators need to

¹ See <http://www4.od.nih.gov/oba/rac/ic/>.

explain the rationale for long-term follow-up, the specific follow-up activities planned, how long follow-up will continue, and what, if any, procedures participants will be asked to undergo. As with any research covered by the Common Rule, participants have the right to withdraw from the study at any time, including during follow-up.

Autopsy

The *NIH Guidelines* state that investigators should inform subjects that an autopsy will be requested at the time of death, no matter what the cause, to obtain vital information about the safety and efficacy of gene transfer. Subjects should be asked to advise their families of the request and of its scientific and medical importance. During the informed consent process, the investigator should explain that the subject is not being asked at this time to consent to autopsy, nor is it required for study participation. However, subjects should be encouraged to express their wishes about an autopsy to their families so that family members are prepared to consider it at the time of the subject's death.

Community Risks

As noted earlier, one theoretical risk of gene transfer is that the vector and the gene it carries could be passed on to close contacts through infection, thus exposing other individuals and the community to risk. The *NIH Guidelines* require that investigators describe in the protocol any potential benefits and hazards of the proposed gene transfer to persons other than the human subjects receiving the experimental intervention. Specifically, investigators must address whether there is a significant possibility that the inserted DNA will spread from the human subject to other persons or to the environment and what measures will be undertaken to mitigate any public health risks. The IBC should be involved in assessment of community health risks.

National Interest in Field and Safety Data

Given the high degree of public interest in gene transfer research, the local or national media may seek information on or interviews with study participants. Investigators must be sensitive to the needs and interests of participants, both when public interest arises from positive information and when it arises from adverse events. Potential participants should be informed that every effort will be made to keep personal information confidential, but it is unwise to imply that the media will never discover or report the identity of individuals. Moreover, sometimes research participants may choose to permit disclosure of their identities and even to participate in media coverage. Therefore, investigators should discuss the circumstances in which information would be provided to the media. Investigators also should

acknowledge that sometimes disclosure of only a small amount of information might lead to the identification of a participant.

Participants also should be informed that adverse events that they may experience might be discussed at a public RAC meeting as part of a process to understand the significance of the event and its implications for the safety of the trial. Although personally identifying information is not conveyed to NIH or at these meetings, the rarity or significance of the event may lead to public interest in more details.

Reproductive Considerations

Some vectors used in gene transfer experiments have the capacity to integrate and alter the germline. When data are inadequate to rule out the possibility of inadvertent germline alteration, nonsterile participants should be informed that the biological consequences of this procedure are not known and that, therefore, unborn children, children who are being breastfed, and pregnant women could be harmed. Discussion of the risk of reproductive harm should be study specific. Study-specific factors include, but are not limited to, frequency of pregnancy testing and the possibility of inadvertent germline effects that could be teratogenic.

Reproductive considerations may be unique to one gender or may need to be discussed differently for men and women. It may be worthwhile to have separate sections in the consent form for those issues pertinent to men and women.

To avoid the possibility of causing harm or abnormalities to an unborn child or horizontal transmission of the vector-transgene combination to sexual partners, participants should be encouraged to practice abstinence for an appropriate length of time or, at a minimum, to use certain contraception methods. The short- and long-term advantages and disadvantages of different contraceptive methods should be explained. In some studies, sperm or ova banking, which may involve an additional cost to the participant, may be advisable.

**counseling
regarding
potential harm**

Under some circumstances, women who are pregnant or lactating may not be eligible to participate in gene transfer trials that pose risks of reproductive harm. (See Chapter 21 for a fuller discussion of the special protections under Subpart B of 45 CFR 46.) When such exclusions are justified, investigators should inform potential subjects that they will be tested to rule out pregnancy. In some gene transfer studies, women who are breastfeeding may not be eligible for participation or may be asked to stop breastfeeding during and for a specified period after study completion.

Investigators should discuss with potential participants what would happen in the event of a pregnancy (e.g., long-term monitoring of offspring).

E. Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Research Subjects

Investigators subject to the *NIH Guidelines* who intend to conduct human gene transfer trials must adhere to Appendix M, "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules

into One or More Human Research Participants," of the *NIH Guidelines*. This appendix contains a list of issues and questions that investigators must take into account in developing their trials. When submitting protocols to NIH OBA, investigators must also include statements about how each of these matters will be handled in the course of their trials.

Key portions of Appendix M draw attention to the safety reporting, informed consent, and other human subjects requirements that are particularly salient or unique to human gene transfer research, including those discussed above. For ease of reference, these sections of Appendix M are presented in Appendix 25.A at the end of this chapter.

Key Concepts: Gene Therapy/Human Gene Transfer Research

- At this time, human gene transfer is experimental and has not been approved for clinical use in treating any condition.
- Two agencies, FDA and NIH, provide special oversight of human gene transfer research at the federal level.
- Locally, human gene transfer research is reviewed by IBCs in addition to IRBs. IBCs were established under the *NIH Guidelines* to provide local, institutional oversight of nearly all forms of research utilizing recombinant DNA. Special review and safety reporting requirements highlight the importance of communication and information sharing between these bodies.
- FDA regulates the products evaluated in human gene transfer clinical trials that are intended for sale in the United States and is responsible for reviewing serious adverse events that occur in a gene transfer study.
- NIH's primary role in this field is to evaluate the scientific, safety, and ethical aspects of human gene transfer research and communicate its findings with the scientific community, IRBs and IBCs, and the public.
- The *NIH Guidelines* articulates standards for investigators and institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived from recombinant DNA.
- Appendix M of the *NIH Guidelines* describes points to consider in the design and submission of human gene transfer trials, including registration of protocols with NIH, review procedures of the RAC, conduct of informed consent, and annual and expedited reporting requirements.
- The RAC review process can result in recommendations on scientific (e.g., study design) and ethical (e.g., the adequacy of informed consent) matters, which are provided to the PI following the RAC meeting in a letter prepared by OBA staff.
- IRBs and FDA may review protocols before or after RAC review but will nonetheless be notified of the RAC recommendations. Final IBC approval of human gene transfer studies subject to the *NIH Guidelines* may not occur until after the RAC review process has been completed.

Reference

National Institutes of Health (NIH). 2002. *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. Available at <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>.

Appendix 25.A: Excerpts from Appendix M of the *NIH Guidelines for Research Involving Recombinant DNA Molecules*

Safety Reporting

Appendix M-I-C-4. Safety Reporting

Principal Investigators must submit, in accordance with this section, Appendix M-I-C-4-a and Appendix M-I-C-4-b, a written report on:

- (1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events); and
- (2) any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity. The report must be clearly labeled as a "Safety Report" and must be submitted to the NIH Office of Biotechnology Activities (NIH OBA) and to the local Institutional Biosafety Committee within the timeframes set forth in Appendix M-I-C-4-b.

Principal Investigators should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable.

Principal Investigators may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH OBA of the delegation and of the name(s), address, telephone and fax numbers of the contact(s). The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

The three alternative mechanisms for reporting serious adverse events to the NIH OBA are: by e-mail to oba@od.nih.gov; by fax to 301-496-9839; or by mail to the Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892-7985.

Appendix M-I-C-4-a. Safety Reporting: Content and Format

The serious adverse event report must include, but need not be limited to:

- (1) the date of the event;
- (2) designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports;
- (3) clinical site;
- (4) the Principal Investigator;
- (5) NIH Protocol number;
- (6) FDA's Investigational New Drug (IND) Application number;
- (7) vector type, e.g., adenovirus;
- (8) vector subtype, e.g., type 5, relevant deletions;
- (9) gene delivery method, e.g., in vivo, ex vivo transduction;
- (10) route of administration, e.g., intratumoral, intravenous;
- (11) dosing schedule;
- (12) a complete description of the event;
- (13) relevant clinical observations;
- (14) relevant clinical history;
- (15) relevant tests that were or are planned to be conducted;
- (16) date of any treatment of the event; and
- (17) the suspected cause of the event.

These items may be reported by using the recommended Adverse Event Reporting Template available on NIH OBA's web site at: <http://www4.od.nih.gov/oba/rac/documents1.htm>, the FDA MedWatch forms, or other means provided that all of the above elements are specifically included.

(Continues on following page)

Reports from laboratory animal studies as delineated in Appendix M-I-C-4 must be submitted in a narrative format.

Appendix M-I-C-4-b. Safety Reporting: Time Frames for Expedited Reports

Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH OBA as soon as possible, but not later than 7 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH OBA as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Changes in this schedule are permitted only where, under the FDA IND regulations [21 CFR 312(c)(3)], changes in this reporting schedule have been approved by the FDA and are reflected in the protocol.

If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported to the NIH OBA within 15 days of the determination.

Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event must be reported within 15 calendar days of the sponsor's receipt of the information.

If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event shall be reported to the NIH OBA within 15 calendar days of the determination.

Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Selection of Human Subjects, Informed Consent, and Privacy

Appendix M-II-C. Selection of the Human Subjects

Estimate the number of human subjects to be involved in the proposed study. Describe recruitment procedures and eligibility requirements, paying particular attention to whether these procedures and requirements are fair and equitable. Specifically:

Appendix M-II-C-1.

How many subjects do you plan to involve in the proposed study?

Appendix M-II-C-2.

How many eligible subjects do you anticipate being able to identify each year?

Appendix M-II-C-3.

What recruitment procedures do you plan to use?

Appendix M-II-C-4.

What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

Appendix M-II-C-5.

How will subjects be selected if it is not possible to include all who desire to participate?

(Continues on following page)

Appendix M-III. Informed Consent

Appendix M-III-A.

Communication About the Study to Potential Participants

Appendix M-III-A-1.

Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?

Appendix M-III-A-2.

How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-III-A-3.

What is the length of time that potential participants will have to make a decision about their participation in the study?

Appendix M-III-A-4.

If the study involves pediatric or mentally handicapped subjects, how will the assent of each person be obtained?

Appendix M-III-B. Informed Consent Document

Submission of a human gene transfer experiment to NIH OBA must include a copy of the proposed informed consent document. A separate Informed Consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a "marker" or to enhance the power of immunotherapy for cancer.

Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the Informed Consent document should include the following specific information in addition to any requirements of the DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the Informed Consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the Informed Consent document.

Appendix M-III-B-1. General Requirements of Human Subjects Research

Appendix M-III-B-1-a. Description/Purpose of the Study

The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component.

Appendix M-III-B-1-b. Alternatives

The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches.

Appendix M-III-B-1-c. Voluntary Participation

The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled.

(Continues on following page)

Appendix M-III-B-1-d. Benefits

The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

Appendix M-III-B-1-e. Possible Risks, Discomforts, and Side Effects

There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization.

If verbal descriptors (e.g., “rare,” “uncommon,” or “frequent”) are used to express quantitative information regarding risk, these terms should be explained.

The Informed Consent document should provide information regarding the approximate number of people who have previously received the genetic material under study. It is necessary to warn potential subjects that, for genetic materials previously used in relatively few or no humans, unforeseen risks are possible, including ones that could be severe.

The Informed Consent document should indicate any possible adverse medical consequences that may occur if the subjects withdraw from the study once the study has started.

Appendix M-III-B-1-f. Costs

The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that are not covered by the investigators or the institution involved.

Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.

Appendix M-III-B-2. Specific Requirements of Gene Transfer Research**Appendix M-III-B-2-a. Reproductive Considerations**

To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified. The inclusion of pregnant or lactating women should be addressed.

Appendix M-III-B-2-b. Long-Term Follow-Up

To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study. The Informed Consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The investigator should request that subjects continue to provide a current address and telephone number.

The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

(Continues on following page)

Appendix M-III-B-2-c. Request for Autopsy

To obtain vital information about the safety and efficacy of gene transfer, subjects should be informed that at the time of death, no matter what the cause, permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.

Appendix M-III-B-2-d. Interest of the Media and Others in the Research

To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following: (i) that the institution and investigators will make efforts to provide protection from the media in an effort to protect the participants' privacy, and (ii) that representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating institutions, vector suppliers, etc., will have access to the subjects' medical records.

Appendix M-IV. Privacy

Indicate what measures will be taken to protect the privacy of subjects and their families as well as maintain the confidentiality of research data. These measures should help protect the confidentiality of information that could directly or indirectly identify study participants.

Appendix M-IV-A.

What provisions will be made to honor the wishes of individual human subjects (and the parents or guardians of pediatric or mentally handicapped subjects) as to whether, when, or how the identity of a subject is publicly disclosed?

Appendix M-IV-B.

What provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual subjects?

Chapter 26

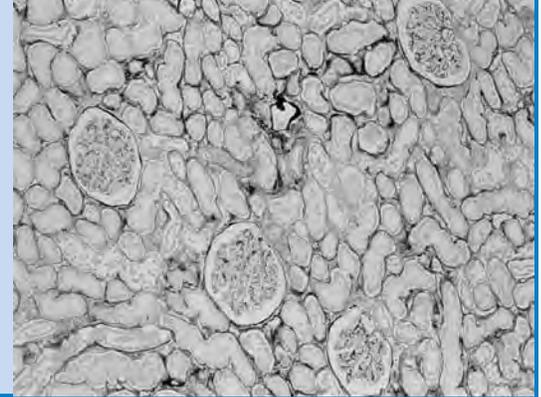
Embryo and Fetal Tissue Research and Human Cloning

- A. Introduction
- B. Fetal Tissue Research
- C. Research with Human Embryos
- D. Human Cloning

Key Concepts

References

Appendix 26.A: Public Law 103-43 Research on Transplantation of Fetal Tissue



A. Introduction

Previous chapters in this resource manual have addressed research that raises unique or heightened concerns and that thus requires extra scrutiny—for example, research with vulnerable populations (Chapter 21), research in emergency or defense-related settings (Chapter 16), international research (Chapter 19), genetic research (Chapter 24), and gene transfer research (Chapter 25). This chapter addresses three additional categories of research that have special additional regulatory or statutory requirements: research involving tissue from aborted fetuses, research involving the *ex utero* human embryo, and research involving human cloning for reproductive purposes. Investigators and Institutional Review Boards (IRBs) must be cognizant of the special conditions under which such research may be conducted and the regulatory and statutory requirements for conducting these types of studies. In some cases, the additional requirements for these categories of research extend above and beyond those required by the Food and Drug Administration (FDA) or the Common Rule.

B. Fetal Tissue Research

Federal law permits funding of some research with cells and tissues from the products of elective as well as spontaneous abortions, and state law facilitates the donation and use of fetal tissue for research. Both state and federal law set forth several requirements for the process of retrieving and using material from this source.

Background

Until 1993, existing federal policy governed only research involving the living fetus *in utero*. When Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in 1974, it placed the topic of research using the human fetus at the top of the commission's agenda. Within four months of assuming office, the commissioners were required to report on the subject, with the proviso that the presentation of their report to the secretary of the Department of Health, Education, and Welfare (DHEW)—now the Department of Health and Human Services (DHHS)—would lift the moratorium that Congress had imposed on federal funding of research on live fetuses *in utero*. In 1975, the National Commission submitted its conclusions and recommendations (National Commission 1975), which formed the basis for regulations that the department issued later that year on research involving fetuses, pregnant women, and human *in vitro* fertilization (IVF) (45 CFR 46, Subpart B).

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

The 1975 provisions remain as elements of the current federal regulations that aim to protect human subjects participating in research conducted with federal funds—rules that also are followed on a voluntary basis by many institutions in the case of research performed without federal support. The special provisions applicable to fetal material

appear in Subpart B, which covers research on

- “the fetus,
- pregnant women, and
- human *in vitro* fertilization” and applies to all DHHS “grants and contracts supporting research, development, and related activities” involving those subjects (45 CFR 46.201(a)).

The regulations primarily address research that could adversely affect living *in utero* fetuses.

Subpart B provides for stringent IRB consideration of proposed research involving fetuses *in utero*, which should be based on the results of preliminary studies on animals and nonpregnant women and on assurances that living

stringent requirements in Subpart B for in utero research

fetuses will be exposed only to minimal risk except when the research is intended to meet the health needs of the fetus or its mother. Specific restrictions also are imposed on the inclusion of pregnant women in research activities. (A more extensive discussion of Subpart B is presented in Chapter 21.)

Section 46.210 of Subpart B states that the sole explicit requirement for research involving “cells, tissues, or organs excised from a *dead fetus*” [*emphasis added*] is that such research “shall be conducted only in accordance with any applicable State or local laws regarding such activities.” Some analysts have argued that this is the *only* component of Subpart B applicable to research in which cells or tissues from dead abortuses are used in research (Areen 1988).

In the 1980s, following extensive animal studies, researchers began experimenting with implanting brain tissue from aborted fetuses into patients with Parkinson’s disease as well as patients with other neurological disorders. National Institutes of Health (NIH) investigators were among those working in this field, and a protocol to use fetal tissue for transplantation research was approved by an internal NIH review body. Although the research complied with Subpart B, the NIH Director sought approval from the Assistant Secretary for Health of DHEW to proceed with the work (Ryan 1991). The result was the imposition of a 1989 moratorium on such work, which was in place until 1993, when the moratorium was lifted by Executive Order. In March of that year, NIH published interim guidelines for research involving human fetal tissue transplantation (OPRR 1994). Provisions to legislate these safeguards were promptly proposed in Congress and were included in the NIH Revitalization Act of 1993, which was signed into law on June 10, 1993.

Federal Law Regarding Research Using Cells and Tissues from Aborted Fetuses

The 1993 Revitalization Act (provided in Appendix 26.A) states that any tissue from any type or category of abortion may be used for research on transplantation, but only for “therapeutic purposes.” Most agree that this means that research on transplantation that has as its goal the treatment of disease is covered by the act but that basic laboratory research—that only tangentially can be described as having a therapeutic purpose—would not be covered.

Under all conditions, the investigator’s research scope is not, however, unfettered. First, research activities in this area must be conducted in accordance with applicable state and local law. The investigator also must obtain a written statement from the donor verifying that:

- she is donating fetal tissue for therapeutic purposes,
- no restrictions have been placed on who the recipient will be, and
- the donor has not been informed of the identity of the recipient.

Furthermore, the attending physician must sign a statement affirming five additional conditions of the abortion, aimed at insulating a woman’s decision to abort from her decision to provide tissue for fetal research.

Finally, the person principally responsible for the experiment also must affirm his/her own knowledge of the sources of tissue, that others involved in the research are aware of the tissue status, and that the researcher had no part in the abortion decision or its timing. The statute provides significant criminal penalties for violation of the following four prohibited acts:

1. Purchase or sale of fetal tissue “for valuable consideration” beyond “reasonable payments [for] transportation, implantation, processing, preservation, quality control, or storage...”
2. Soliciting or acquiring fetal tissue through the promise that a donor can designate a recipient
3. Soliciting or acquiring fetal tissue through the promise that the recipient will be a relative of the donor
4. Soliciting or acquiring fetal tissue after providing “valuable consideration” for the costs associated with the abortion itself (42 USC §§289g-2(a)-(c))

Office for Human Research Protections Guidance

Current Office for Human Research Protections (OHRP) guidance merely reiterates the need for institutions conducting or planning to conduct research involving the transplanta-

tion of human fetal tissue for therapeutic purposes to comply with the law.¹ The guidance states that adherence to an OHRP-approved Human Subject Assurance of Compliance (see Chapter 5) requires that this legislative mandate be met.

FDA Oversight

In a 2000 letter to sponsors and researchers, FDA asserted its jurisdiction over fetal cells and tissues intended for use in humans. The letter states that, “[B]ecause this is an evolving field with a number of issues to resolve, we request that you contact FDA to determine whether any clinical investigations you are conducting, planning or sponsoring would require submission of an Investigational New Drug (IND) application.”² Examples of studies requiring an Investigational New Drug (IND) Application include, but are not limited to, human fetal neuronal cells to treat Parkinson’s disease, fetal retinal tissue to prevent blindness, and fetal spinal cord cells to treat syringomyelia. Clinical trials involving such use of fetal tissues are subject to FDA’s regulations on investigational new drugs, including those for the submission and review of an IND set forth in 21 CFR Part 312. In addition, FDA has published several rules on cellular and tissue-based products.³

State Law Regarding Research Using Aborted Fetuses

As recognized by federal statutes and regulations, state law governs the manner in which cells and tissues from dead fetuses become available for research, principally by statutes, regulations, and case law on organ transplantation. The most basic legal provisions lie in the Uniform Anatomical

Uniform Anatomical Gift Act

Gift Act (UAGA), which was first proposed in 1968 and which rapidly became the most widely adopted uniform statute.

Although the UAGA is largely consistent with relevant federal statutes and regulations and should facilitate researchers obtaining cadaveric fetal tissue, a number of states have adopted other statutes that limit or prohibit certain types of research with fetal remains.

Laws Facilitating Donation of Fetal Material: The UAGA.

The UAGA is relevant not only because federal statutes and regulations explicitly condition funding for research with fetal tissue on compliance with state and local laws but also because the act applies even when research using fetal tissue does not receive federal funding.

The act establishes a system of voluntary donation of “anatomical gifts” for transplantation, education, and re-

search. It was intended to make it easier for people to authorize gifts of their own body (or parts thereof) through a simple “donor card” executed before the occasion arose, as well as to allow donations to be made with the permission of the next-of-kin, following an order established by the statute. The revised UAGA includes “a stillborn infant or fetus” in the definition of *decedents*, for whom parental consent is determinative (UAGA §1(3)). The UAGA also provides that “neither the physician or surgeon who attends the donor at death nor the physician or surgeon who determines the time of death” may be involved in the team that will use the organs removed from the decedent (UAGA §8(b)). This section, although it may be waived, is comparable to the separation that the 1993 NIH Revitalization Act and Subpart B of the DHHS regulations require between the research team and any physicians involved in terminating a pregnancy, determining fetal viability, or assisting in a clinical procedure during which fetal tissue is derived for research purposes (45 CFR 46.206(a)(3)).

However, federal law restricts the procedures authorized by the UAGA in one area. The UAGA permits donors to designate recipients—including individual patients—of anatomical gifts. The stricter provisions of the NIH Revitalization Act (which prohibits a donor from having knowledge of an individual transplant recipient) could override this state law in the case of federally supported fetal tissue transplantation.

Laws Restricting Use of Donated Fetal Material for Research. To diminish the impact that the potential use of a fetus in research might have on the decision to abort, several states have enacted many restrictions on payment for fetal remains. The broadest prohibitions appear as part of state statutes regulating or prohibiting fetal research. The most widely adopted prohibitions on the commercialization of fetal remains are those in §§10(a) and (b) of the 1987 revision of the UAGA, which prohibit the sale or purchase of any human body parts for any consideration beyond that necessary to pay for expenses incurred in the removal, processing, and transportation of the tissue. On the federal level, what is in essence the same proscription is included both in the 1993 NIH Revitalization Act, which bars the acquisition or transfer of fetal tissue for “valuable consideration” with the same exceptions (42 USC 289g-2(a)), and in the National Organ Transplant Act of 1984 (NOTA; 42 USC §274e(a) and 4(e)(c)(2)), which prohibits the sale of any human organ for “valuable consideration for use in human transplantation” if the sale involves interstate commerce. In 1988, Congress amended NOTA to include fetal organs within the definition of *human organ*, in order to foreclose the sale of fetal tissue as well (42 USC §274(e)(c)(1)).

¹ Available at www.hhs.gov/ohrp/humansubjects/guidance/fetal.pdf.

² See www.fda.gov/cber/ltr/fetal113000.htm.

³ See www.fda.gov/cber/rules/frtisreg012103.htm and www.fda.gov/cber/rules/frtisreg011901.htm.

C. Research with Human Embryos

Federally supported scientists are prohibited by law from experimentation involving the human embryo; however, research conducted in the private sector takes place without any federal oversight.

Federal law regarding research using human embryos by investigators employed or funded by the federal government may best be understood by reviewing Subpart B of the DHHS policy on the protection of human subjects and the rider that has been attached for several years to the DHHS appropriation, most recently in the Omnibus Consolidated and Emergency Supplemental Appropriations Act for Fiscal Year 1999 (Public Law [PL] 105-277, 112 Stat. 2681).

Background

Subpart B originated in concerns about research on the human fetus, but it also applies to “grants and contracts supporting research, development, and related activities involving...human *in vitro* fertilization” (45 CFR 46.201(a)). At the time these provisions were first promulgated, *in vitro* fertilization (IVF) was still an experimental technique. Recognizing that U.S. scientists might pursue research on IVF and the earliest stages of human development, the regulations provided that “no application or proposal involving human *in vitro* fertilization may be funded by the Department [until it] has been reviewed by the Ethics Advisory Board (EAB) and the Board has rendered advice as to its acceptability from an ethical standpoint.”⁴

In 1977, the Secretary of DHEW, asked the newly appointed EAB to study the broader social, legal, and ethical issues raised by human IVF. In its 1979 report to the secretary, the EAB concluded that federal support for IVF research was “acceptable from an ethical standpoint” provided that certain conditions were met, such as informed consent for the use of gametes, an important scientific goal “not reasonably attainable by other means,” and not maintaining an embryo “*in vitro* beyond the stage normally associated with the completion of implantation (14 days after fertilization)” (DHEW EAB 1979, 106, 107). No action was ever taken by the Secretary with respect to the board’s report, and the department dissolved the EAB in 1980.

Because the department did not appoint another EAB to consider additional research proposals, a *de facto* moratorium on such research took effect. The Revitalization Act of

1993 effectively ended the moratorium on IVF and other types of research funded by DHHS involving human embryos by nullifying the regulatory provision that mandated EAB review.

However, Congress attached a rider to that year’s DHHS appropriations bill, which has been in place every year since, that stipulates that none of the DHHS funds appropriated could be used to support any activity involving

- “the creation of a human embryo or embryos for research purposes; or
- research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero* under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 USC 289g(b)).”

This rider is still in effect for all DHHS-sponsored research. It does not apply to other federal research agencies.

Use of Human Embryos for Stem Cell Research

When human embryonic stem cells were first isolated using private funds, the applicability of the congressional prohibition on human embryo research conducted with federal funds was reviewed by the DHHS General Counsel, who concluded that the prohibition did not prevent NIH from supporting research that uses embryonic stem cells derived from human embryos because the cells themselves do not meet the statutory, medical, or biological definition of a human embryo (NIH OD 1999). Having concluded that NIH could fund intramural and extramural research that utilizes but does not create human embryonic stem cells, NIH delayed funding until an advisory group developed guidelines for the ethical conduct of research in this area (NIH 1999).

However, on August 9, 2001, at 9:00 p.m. EDT, the President announced his decision to allow federal funds to be used for research on existing human embryonic stem cell lines as long as “prior to his announcement (1) the derivation process (which commences with the removal of the inner cell mass from the blastocyst) had already been initiated and (2) the embryo from which the stem cell line was derived no longer had the possibility of development as a human being.”⁵

⁴ 45 CFR § 46.204(d), nullified by section 121(c) of the NIH Revitalization Act of 1993, PL 103-43, June 10, 1993; see *Federal Register* 59: 28276 (June 1, 1994).

⁵ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>.

In addition, the President established the following criteria that must be met:

- the stem cells must have been derived from an embryo that was created for reproductive purposes
- the embryo was no longer needed for these purposes
- informed consent must have been obtained for the donation of the embryo
- no financial inducements were provided for donation of the embryo

To facilitate research using human embryonic stem cells, NIH created a Human Embryonic Stem Cell Registry that lists the human embryonic stem cells that meet the eligibility criteria. Specifically, the laboratories or companies that provide the cells listed on the registry submit a signed assurance to NIH. Each provider must retain for submission to NIH, if necessary, written documentation to verify the statements in the signed assurance.

**Human
Embryonic
Stem Cell
Registry**

The registry is accessible to investigators at escr.nih.gov. Requests for federal funding must cite a human embryonic stem cell line that is listed on the registry. Such requests also will need to meet existing scientific and technical merit criteria and be recommended for funding by the relevant NIH National Advisory Council, as appropriate.⁶

OHRP Guidance/FDA Regulations

Guidance issued by OHRP in 2002⁷ addresses the regulatory controls that apply to research involving human embryonic stem cells or germ cells. (Germ cells are stem cells derived from fetal gonadal tissue.) As with research involving fetal tissue, the guidance reminds investigators and institutions that federally funded research using these cells must be conducted in compliance with the Common Rule, including the President's criteria (described above). However, the guidance points out that *in vitro* research and research in animals using already derived and established human cell lines, from which the identity of the donor(s) cannot readily be obtained by the investigator, are not considered human subjects research and are not governed by the DHHS or FDA regulations. Moreover, IRB review is not needed for such research. If, however, the cells retain links to identifying information, the regulations apply.

The guidance goes on to clarify that *in vitro* research or research in animals using a human cell line that retains a link to identifying information ordinarily would not be consid-

ered human subjects research if:

- the investigator and research institution do not have access to identifiable private information related to the cell line; and
- a written agreement is obtained from the holder of the identifiable private information related to the cell line providing that such information will not be released to the investigator under any circumstances. In this case, the research may be considered to not involve human subjects because the identity of the donor(s) could not be "readily ascertained" by the investigator or associated with the cell line. Under such circumstances, an institution or an IRB could determine that IRB review of the research using the cell line was not needed.

Intervention or Interactions with the Individual. OHRP guidance states that all DHHS-conducted or supported clinical research that involves interactions with living individuals, including the transplantation of human cells or test articles, such as differentiated cells derived from human embryos or human fetal tissue, into human recipients is human subjects research subject to the Common Rule because recipients are human subjects. As such, IRB review and approval is required for such research.

Furthermore, all clinical research involving the use of cells or test articles regulated by FDA as drugs, devices, and biological products is subject to regulation and oversight by FDA. This clinical research must be conducted in compliance with FDA's regulations governing INDs or Investigational Device Exemptions (IDEs) regardless of source of funding. All human studies conducted under INDs and IDEs are subject to FDA's IRB and informed consent regulations.

In addition, other federal, state or local laws may also apply to transplantation or other research involving these cells or test articles.

State Law Regarding Research Using Cells and Tissues from Human Embryos

State laws tend to be more focused on regulating and restricting research using human fetuses or their remains than on research involving laboratory manipulation of human gametes and early stage embryos. Nonetheless, although the statutes usually are silent on issues specific to IVF (other than commercialization), some could be interpreted broadly enough to encompass a range of experimental activities involving IVF, including cryopreservation, preimplantation screening, gene therapy, twinning, cell line development, and basic research (Coleman 1996). Moreover, some states prohibit embryo research altogether. It is critical that re-

⁶ Further guidance is accessible at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html>.

⁷ See www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf.

searchers and institutions conducting research with human embryonic material become familiar with state laws because they apply regardless of the source of funding for the research.

The subject of commercialization is a potentially important one, affecting both researchers who must acquire embryos from for-profit IVF clinics or other sources and downstream users who may develop derivative, commercial applications from basic embryological and stem cell research. Most states prohibit payment for IVF embryos for research purposes.

D. Human Cloning

Despite numerous attempts by Congress to prohibit human cloning for the purposes of reproduction, no legislation has yet been signed into law.

In 1997, President Clinton issued a memorandum for the heads of executive departments and agencies prohibiting federal funding for the cloning of human beings. The memorandum noted that the existing restrictions on the use of federal funds for research involving human embryos do not fully assure this result.

In 1998, FDA sent a “Dear Colleague” letter to IRBs confirming that the agency has jurisdiction over clinical research using cloning technology to create a human being and to inform IRBs of the FDA regulatory process that is required before any investigator can proceed with such a clinical investigation.⁸ The letter states the following:

Clinical research using cloning technology to create a human being is subject to FDA regulation under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. Under these statutes and FDA’s implementing regulations, before such research may begin, the sponsor of the research is required to submit to FDA an IND describing the proposed research plan; to obtain authorization from a properly constituted and functioning IRB; and to obtain a commitment from the investigators to obtain informed consent from all human subjects of the research. Such research may proceed only when an IND is in effect. Since FDA believes that there are major unresolved safety questions pertaining to the use of cloning technology to create a human being, until those questions are appropriately addressed in the IND, FDA would not permit any such investigation to proceed.

⁸ Available at www.fda.gov/cber/ltr/aaclone.pdf.

Key Concepts: Embryo and Fetal Tissue Research and Human Cloning

- The 1993 Revitalization Act states that any tissue from any type or category of abortion may be used for research on transplantation but only for “therapeutic purposes.”
- Investigators conducting fetal tissue research must obtain a written statement from the donor verifying that
 - she is donating fetal tissue for therapeutic purposes,
 - no restrictions have been placed on who the recipient will be, and
 - the donor has not been informed of the identity of the recipient. Furthermore, the attending physician must sign a statement affirming five additional conditions of the abortion, aimed at insulating a woman’s decision to abort from her decision to provide tissue for fetal research.
- The individual principally responsible for a fetal tissue experiment must affirm his or her own knowledge of the sources of tissue, that others involved in the research are aware of the tissue status, and that the researcher had no part in the abortion decision or its timing.
- The statute governing fetal tissue research imposes criminal penalties for the purchase or sale of material, soliciting or acquiring fetal tissue through the promise that a donor can designate a recipient, soliciting or acquiring fetal tissue through the promise that the recipient will be a relative of the donor, or soliciting or acquiring fetal tissue after providing “valuable consideration” for the costs associated with the abortion itself.
- FDA has jurisdiction over fetal cells and tissues intended for use in humans.
- As recognized by federal statutes and regulations, state law governs the manner in which cells and tissues from dead fetuses become available for research, principally by statutes, regulations, and case law on organ transplantation. The most basic legal provisions lie in the UAGA.
- A rider to the DHHS appropriations bill stipulates that none of the DHHS funds appropriated can be used to support any activity involving
 - “the creation of a human embryo or embryos for research purposes; or
 - research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses *in utero*.”
- Federal funds can be used for research on existing human embryonic stem cell lines as long as the derivation process (which commences with the removal of the inner cell mass from the blastocyst) was initiated prior to August 9, 2001, 9:00 p.m. EDT, and the embryo from which the stem cell line was derived no longer had the possibility of development as a human being.
- Any research use of embryonic stem cells for transplantation requires IRB review.
- FDA has jurisdiction over embryonic cells and tissues intended for use in humans.
- State laws vary as to their permissiveness regarding embryo research.

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**Appendix 26.A:
Public Law 103-43; June 10, 1993
National Institutes of Health Revitalization Act of 1993
Title I - General Provisions Regarding Title IV of Public Health Service Act
Subtitle A - Research Freedom
PART II - Research on Transplantation of Fetal Tissue**

SEC. 111. ESTABLISHMENT OF AUTHORITIES.

Part G of title IV of the Public Health Service Act (42 U.S.C. 289 et seq.) is amended by inserting after section 498 the following section:

RESEARCH ON TRANSPLANTATION OF FETAL TISSUE

SEC. 498A.

(a) ESTABLISHMENT OF PROGRAM-

- (1) IN GENERAL** - The Secretary may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes.
- (2) SOURCE OF TISSUE** - Human fetal tissue may be used in research carried out under paragraph (1) regardless of whether the tissue is obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.

(b) INFORMED CONSENT OF DONOR-

- (1) IN GENERAL** - In research carried out under subsection (a), human fetal tissue may be used only if the woman providing the tissue makes a statement, made in writing and signed by the woman, declaring that—
 - (A)** the woman donates the fetal tissue for use in research described in subsection (a);
 - (B)** the donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue; and
 - (C)** the woman has not been informed of the identity of any such individuals.
- (2) ADDITIONAL STATEMENT** - In research carried out under subsection (a), human fetal tissue may be used only if the attending physician with respect to obtaining the tissue from the woman involved makes a statement, made in writing and signed by the physician, declaring that—
 - (A)** in the case of tissue obtained pursuant to an induced abortion—
 - (i) the consent of the woman for the abortion was obtained prior to requesting or obtaining consent for a donation of the tissue for use in such research;
 - (ii) no alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue; and
 - (iii) the abortion was performed in accordance with applicable State law;
 - (B)** the tissue has been donated by the woman in accordance with paragraph (1); and
 - (C)** full disclosure has been provided to the woman with regard to—
 - (i) such physician's interest, if any, in the research to be conducted with the tissue; and
 - (ii) any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care.

(c) INFORMED CONSENT OF RESEARCHER AND DONEE - In research carried out under subsection (a), human fetal tissue may be used only if the individual with the principal responsibility for conducting the research involved makes a statement, made in writing and signed by the individual, declaring that the individual—

- (1)** is aware that
 - (A)** the tissue is human fetal tissue;
 - (B)** the tissue may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth; and
 - (C)** the tissue was donated for research purposes;
- (2)** has provided such information to other individuals with responsibilities regarding the research;
- (3)** will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and
- (4)** has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.

(Continued on following page)

(d) AVAILABILITY OF STATEMENTS FOR AUDIT-

- (1) IN GENERAL** - In research carried out under subsection (a), human fetal tissue may be used only if the head of the agency or other entity conducting the research involved certifies to the Secretary that the statements required under subsections (b)(2) and (c) will be available for audit by the Secretary.
- (2) CONFIDENTIALITY OF AUDIT** - Any audit conducted by the Secretary pursuant to paragraph (1) shall be conducted in a confidential manner to protect the privacy rights of the individuals and entities involved in such research, including such individuals and entities involved in the donation, transfer, receipt, or transplantation of human fetal tissue. With respect to any material or information obtained pursuant to such audit, the Secretary shall—
 - (A)** use such material or information only for the purposes of verifying compliance with the requirements of this section;
 - (B)** not disclose or publish such material or information, except where required by Federal law, in which case such material or information shall be coded in a manner such that the identities of such individuals and entities are protected; and
 - (C)** not maintain such material or information after completion of such audit, except where necessary for the purposes of such audit.

(e) APPLICABILITY OF STATE AND LOCAL LAW-

- (1) RESEARCH CONDUCTED BY RECIPIENTS OF ASSISTANCE** - The Secretary may not provide support for research under subsection (a) unless the applicant for the financial assistance involved agrees to conduct the research in accordance with applicable State law.
- (2) RESEARCH CONDUCTED BY SECRETARY** - The Secretary may conduct research under subsection (a) only in accordance with applicable State and local law.

(f) REPORT- The Secretary shall annually submit to the Committee on Energy and Commerce of the House of Representatives, and to the Committee on Labor and Human Resources of the Senate, a report describing the activities carried out under this section during the preceding fiscal year, including a description of whether and to what extent research under subsection (a) has been conducted in accordance with this section.

(g) DEFINITION- For purposes of this section, the term 'human fetal tissue' means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a 'stillbirth.'

SEC. 112. PURCHASE OF HUMAN FETAL TISSUE; SOLICITATION OR ACCEPTANCE OF TISSUE AS DIRECTED DONATION FOR USE IN TRANSPLANTATION.

Part G of title IV of the Public Health Service Act, as amended by section 111 of this Act, is amended by inserting after section 498A the following section:

PROHIBITIONS REGARDING HUMAN FETAL TISSUE

SEC. 498B.

(a) PURCHASE OF TISSUE- It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration if the transfer affects interstate commerce.

(b) SOLICITATION OR ACCEPTANCE OF TISSUE AS DIRECTED DONATION FOR USE IN TRANSPLANTATION -

It shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purpose of transplantation of such tissue into another person if the donation affects interstate commerce, the tissue will be or is obtained pursuant to an induced abortion, and—

- (1)** the donation will be or is made pursuant to a promise to the donating individual that the donated tissue will be transplanted into a recipient specified by such individual;
- (2)** the donated tissue will be transplanted into a relative of the donating individual; or
- (3)** the person who solicits or knowingly acquires, receives, or accepts the donation has provided valuable consideration for the costs associated with such abortion.

(Continued on following page)

(c) CRIMINAL PENALTIES FOR VIOLATIONS -

- (1) IN GENERAL** - Any person who violates subsection (a) or (b) shall be fined in accordance with title 18, United States Code, subject to paragraph (2), or imprisoned for not more than 10 years, or both.
- (2) PENALTIES APPLICABLE TO PERSONS RECEIVING CONSIDERATION** - With respect to the imposition of a fine under paragraph (1), if the person involved violates subsection (a) or (b)(3), a fine shall be imposed in an amount not less than twice the amount of the valuable consideration received.

(d) DEFINITIONS - For purposes of this section:

- (1)** The term 'human fetal tissue' has the meaning given such term in section 498A(f).
- (2)** The term 'interstate commerce' has the meaning given such term in section 201(b) of the Federal Food, Drug, and Cosmetic Act.
- (3)** The term 'valuable consideration' does not include reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue.

SEC. 113. NULLIFICATION OF MORATORIUM.

(a) IN GENERAL - Except as provided in subsection (c), no official of the executive branch may impose a policy that the Department of Health and Human Services is prohibited from conducting or supporting any research on the transplantation of human fetal tissue for therapeutic purposes. Such research shall be carried out in accordance with section 498A of the Public Health Service Act (as added by section 111 of this Act), without regard to any such policy that may have been in effect prior to the date of the enactment of this Act.

(b) PROHIBITION AGAINST WITHHOLDING OF FUNDS IN CASES OF TECHNICAL AND SCIENTIFIC MERIT -

- (1) IN GENERAL** - Subject to subsection (b)(2) of section 492A of the Public Health Service Act (as added by section 101 of this Act), in the case of any proposal for research on the transplantation of human fetal tissue for therapeutic purposes, the Secretary of Health and Human Services may not withhold funds for the research if—
 - (A)** the research has been approved for purposes of subsection (a) of such section 492A;
 - (B)** the research will be carried out in accordance with section 498A of such Act (as added by section 111 of this Act); and
 - (C)** there are reasonable assurances that the research will not utilize any human fetal tissue that has been obtained in violation of section 498B(a) of such Act (as added by section 112 of this Act).
- (2) STANDING APPROVAL REGARDING ETHICAL STATUS** - In the case of any proposal for research on the transplantation of human fetal tissue for therapeutic purposes, the issuance in December 1988 of the Report of the Human Fetal Tissue Transplantation Research Panel shall be deemed to be a report— (A) issued by an ethics advisory board pursuant to section 492A(b)(5)(B)(ii) of the Public Health Service Act (as added by section 101 of this Act); and (B) finding, on a basis that is neither arbitrary nor capricious, that the nature of the research is such that it is not unethical to conduct or support the research.

(c) AUTHORITY FOR WITHHOLDING FUNDS FROM RESEARCH - In the case of any research on the transplantation of human fetal tissue for therapeutic purposes, the Secretary of Health and Human Services may withhold funds for the research if any of the conditions specified in any of subparagraphs (A) through (C) of subsection (b)(1) are not met with respect to the research.

(d) DEFINITION - For purposes of this section, the term 'human fetal tissue' has the meaning given such term in section 498A(f) of the Public Health Service Act (as added by section 111 of this Act).

Chapter 27

Agency Chapter U.S. Department of Energy

- A. Introduction
- B. Department of Energy Resources



A. Introduction

The Department of Energy (DOE) and its predecessor agencies (the Atomic Energy Commission [AEC]; the Energy Research and Development Administration) traditionally have considered the health of workers in its facilities to be a basic responsibility. From its inception, the U.S. nuclear program measured worker exposures and their impacts on worker health. Post-World War II studies involving active workers were governed by the ethical principles of medical and human research practices as set forth in the internationally accepted *Nuremberg Code* of 1949.

Paralleling these interests and the continued involvement of workers as research subjects was an increasing concern and interest among the more developed countries in the protection of human subjects from research risks. This trend reflected increasing concerns for human rights and developing technologies that enabled the detection of biological injury or abnormalities at the cellular level in the absence of clinical signs or symptoms and growing capabilities to compile and manipulate large electronic databases. Accordingly, AEC initially encouraged and by 1970 required its contractors engaged in such work to comply with regulations then being developed by the National Institutes of Health (NIH) to protect human subjects involved in NIH-sponsored research. Contractor institutions set about establishing their own Institutional Review Boards (IRBs) or making arrangements with existing IRBs to provide the necessary reviews of human studies protocols in order to assure the physical protection and informed consent of research subjects. There was, however, a growing tendency during the late 1970s and early 1980s for the protocols for such studies to be submitted to the responsible IRB for review as a matter of record. This was a period of rapid development of increasingly sophisticated technologies enabling the detection of genetic patterns and aberrations known to be, or suspected of being, associated with existing

disease or predictors of disease whose clinical significance was unknown or incomplete. With them, new and more complex ethical concerns continued to emerge in the 1990s, requiring increased efforts by DOE to maintain an adequate level of monitoring and research human subjects protection. Such efforts resulted in the establishment of a comprehensive policy for the protection of human subjects in research.

Policy: Purpose and Scope

DOE's research portfolio is unique among agencies supporting research because of its breadth (e.g., nuclear fission to human biology). Research on human subjects performed in accordance with ethical and humanitarian principles allows experiments to be performed that provide medical and scientific benefits to individuals and to the nation. Such research using human subjects encompasses a broader range of research than many investigators, program managers, and government officials often realize. In addition to traditional biomedical and clinical studies, human subjects research includes, but is not limited to, studies that use, create, or collect:

- humans to test devices, products, or materials developed through research; to examine human-machine interfaces; or to evaluate environmental alterations
- bodily materials such as cells, blood, tissues, or urine that are identifiable with individuals even if the materials were not collected for the study in question
- private information readily identifiable with individuals, including genetic information and medical and exposure records, such as worker health studies, even if the information was not collected specifically for the study in question
- identifiable or high-risk data, including surveys, collected through direct intervention or interaction with individuals

- studies conducted to gain generalizable knowledge about categories or classes of subjects (e.g., worker populations or subgroups)

Established Policy

All research conducted at DOE institutions, supported with DOE funds, or performed by DOE employees, including research that is classified and proprietary, whether done domestically or in an international environment, must comply with all federal regulations and DOE requirements that address the protection of human subjects. These include:

- 10 CFR Part 745, DOE, Protection of Human Subjects;
- 45 CFR Part 46, Department of Health and Human Services, Protection of Human Subjects; and
- DOE O 443.1A, Protection of Human Subjects.

No research involving human subjects conducted with DOE funding, at DOE institutions, or by DOE personnel may be initiated without both a project assurance and approval by the cognizant IRB in accordance with 10 CFR 745.103.

Any new assurance must be an Office for Human Research Protections Federalwide Assurance. These requirements must be met before any research involving human subjects is initiated. Other responsibilities and requirements are found in:

- DOE O 443.1A, Policy on the Protection of Human Subjects, of 12-20-07, which defines the DOE policy for the protection of human subjects in research activities.
- DOE O 443.1A, Protection of Human Subjects, of 12-20-07, which defines the implementation of the policy for the protection of human subjects in research activities.¹

B. DOE Resources

DOE Human Subjects Working Group

A 1988 gathering of IRB administrators and chairpersons attended the first meeting of DOE's Human Subjects Working Group (HSWG) was to

Human Subjects Working Group

be the beginning of what would become a strongly influential group comprised of DOE field and headquarters officials, IRB members, program and project managers, other government agency officials (NIH, National Institute for Occupational Safety and Health), university and hospital staff, various experts, and former DOE workers.

The HSWG was created as an umbrella group providing educational and networking opportunities for the DOE human subjects community. Thus, the HSWG formalized DOE's commitment to protecting human subjects in research studies. The DOE human subjects program manager is also the chairperson of the HSWG.²

A review of HSWG activities since its inception may provide some guidance and counsel regarding human subjects protection issues as viewed by DOE.³

A listing of the human subjects regulations, orders, policy statements, and legislation applicable to DOE can be found at <http://humansubjects.energy.gov/regulations/default.htm>.

A listing of DOE sites with human subjects activities, their assurances and agreements to perform such work, their IRB chairpersons or non-DOE institution, and their IRB administrator or contact is provided at <http://humansubjects.energy.gov/doe-resources/assurances.htm>.

DOE Human Subjects Research Database

The DOE Human Subjects Research Database contains information relating to research projects involving human subjects (projects reviewed by an IRB and not given exemption status) that are currently funded by DOE or are performed at DOE facilities with support from other sponsors or are performed by DOE personnel or DOE contractor personnel. This database consists of a searchable interface, detailed descriptions of each research project, and a section that summarizes the information for quick referencing. Currently the database is administered by the Oak Ridge Institute for Science and Education.⁴

Human Subjects Research Database

¹ Both documents are available at <http://humansubjects.energy.gov/regulations/default.htm>.

² The most complete historical information about the HSWG is found in the Winter 1999/2000 issue of the DOE "Protecting Human Subjects" newsletter on pages 14 and 17-18 at <http://humansubjects.energy.gov/doe-resources/newsletter/Winter00.pdf>. Other historical information can be found at <http://humansubjects.energy.gov/doe-resources/newsletter/fall94-newsltr.pdf>; <http://humansubjects.energy.gov/doe-resources/newsletter/winter96-newsltr.pdf>; <http://humansubjects.energy.gov/doe-resources/newsletter/spring97-newsltr.pdf>; and <http://humansubjects.energy.gov/doe-resources/newsletter/default.htm>.

³ Details about the working group members and how to contact them can be found at <http://humansubjects.energy.gov/default.htm>.

⁴ Search for more information about the database, and retrieve data for the years 1994 through 2004 by visiting <http://hsrd.ornl.gov/>.

Consent Forms

A guide to the understanding and preparation of consent forms and other related information can be obtained at www.science.doe.gov/ober/humsubj/irb's.html.

Education and Training for Human Subjects Research

DOE Protecting Human Subjects Newsletter. The newsletter is an essential part of the educational outreach of the DOE human subjects research program that addresses current issues and concerns about human research supported by DOE. It focuses on DOE laboratories and specific issues DOE laboratories face while conducting human subjects research at their facilities. The newsletter often refers the reader to materials or informational contacts that may provide further guidance on human subjects research. The newsletter also announces upcoming meetings and other events that cover human research topics.⁵

Collaborative IRB Training Initiative Human Subjects Training Program. In order to ensure that every laboratory and individual involved in human subjects research has the appropriate training, DOE has developed an educational

module that provides an understanding of the rules, ethics, and practices that are required in order to conduct research with human subjects. The intent of this educational activity is to enhance the quality of these research projects and forestall any potential problems with research on human subjects that is being conducted at DOE sites.⁶

Community IRB Members. “The Community IRB Member: Neighbor & Partner” is a Web site for enhancing communication and providing resources for and about community IRB members, who are critical to the protection of human subjects. These members represent a nationwide resource that needs to be acknowledged and strengthened.⁷

⁵ The current newsletter along with archived copies can be accessed at www.science.doe.gov/ober/humsubj/newslett.html. Subscriptions to the newsletter from interested parties also may be entered at this site.

⁶ See www.citiprogram.org/default.asp.

⁷ See www.ornl.gov/communityirb/.

Appendix A

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

- A. Boundaries Between Practice and Research
- B. Basic Ethical Principles
- C. Applications

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner. The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects. This statement consists

of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research” are not carefully defined. For the most part, the term “practice” refers to interventions that are designed solely to enhance the well being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term “research” designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself,

constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression “basic ethical principles” refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethic of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons

Respect for persons incorporates at least two ethical convictions; first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons’ considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person’s considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so. However, not every human being is capable of self determination. The capacity for self-determination matures during an individual’s life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations. In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to “volunteer” or to “protect” them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence

Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term “beneficence” is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense:

- 1) do not harm and
- 2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim “do no harm” has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients “according to their best judgment.” Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it

is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to give forethought to the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic and social procedures. The principle of beneficence often occupies a well defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries.

Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of “fairness in distribution” or “what is deserved.” An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of

just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit. Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available. Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conflict of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent

Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed

consent are satisfied. While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information

Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc. However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that

- 1) incomplete disclosure is truly necessary to accomplish the goals of the research,
- 2) there are no undisclosed risks to subjects that are more than minimal, and

- 3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them.

Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension

The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice. Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the preservation of the information to the subject's capabilities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension. Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm. The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness

An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable. Unjustifiable pressures usually occur when persons in positions of authority or commanding influence—especially where possible sanctions are involved—urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits

The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits

The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm. The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted

with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harms and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked. Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).

Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits

It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, specially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability

of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations:

- (i) Brutal or inhumane treatment of human subjects is never morally justified.
- (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures.
- (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation).
- (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.
- (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness; thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only “undesirable” persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the

appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects. Even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus, injustice arises from social, racial, sexual, and cultural biases institutionalized in society. Even if individual researchers are treating their research subjects fairly, and IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting. They can consider distributive justice in selecting research subjects. Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Appendix B

Federal Policy for the Protection of Human Subjects; Notices and Rules

Federal Register. Vol. 56. No. 117 (June 18, 1991), pp 28002-28007.

Final Report Federal Register

Tuesday
June 18, 1991

Part II

Federal Policy for the Protection of Human Subjects; Notices and Rules

Office of Science and Technology Policy
Department of Agriculture
Department of Energy
National Aeronautics and Space Administration
Department of Commerce
Consumer Product Safety Commission
International Development Cooperation Agency
 Agency for International Development
Department of Housing and Urban Development
Department of Justice
Department of Defense
Department of Education
Department of Veterans Affairs
Environmental Protection Agency
Department of Health and Human Services
 Office of the Secretary
 Food and Drug Administration
National Science Foundation
Department of Transportation

Editorial Note: This reprint incorporates a correction document published in the **Federal Register** of June 28, 1991.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Federal Policy for the Protection of Human Subjects

AGENCY: Office of Science and Technology Policy, Executive Office of the President.

ACTION: Notice of Federal Policy for Protection of Human Subjects.

SUMMARY: The Office of Science and Technology Policy has accepted the

Final Federal Policy for the Protection of Human Subjects in the form of the common rule promulgated in this issue of the **Federal Register**. The common rule was developed by the Interagency Human Subjects Coordinating Committee of the Federal Coordinating Council for Science, Engineering and Technology, in response to public comment on the notice of proposed policy for Department and Agency Implementation published in the **Federal Register** on November 10, 1988 (53 FR 45660).

Note that the Central Intelligence Agency is required by Executive Order

12333 to conform to the guidelines issued by the Department of Health and Human Services (HHS).

ADDRESSES: Requests for additional information should be addressed to Dr. Joan P. Porter, Interagency Human Subjects Coordinating Committee, Building 31, room 5B59, Bethesda, Maryland 20892, Telephone: (301) 496-7005.

D. Allan Bromley,

Director, Office of Science and Technology Policy, Executive Office of the President.

[FR Doc. 91-14257 Filed 6-17-91; 8:45 am]

BILLING CODE 3170-01-M

DEPARTMENT OF AGRICULTURE

7 CFR Part 1c

DEPARTMENT OF ENERGY

10 CFR Part 745

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

14 CFR Part 1230

DEPARTMENT OF COMMERCE

15 CFR Part 27

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1028

INTERNATIONAL DEVELOPMENT COOPERATION AGENCY

Agency for International Development

22 CFR Part 225

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

24 CFR Part 60

DEPARTMENT OF JUSTICE

28 CFR Part 46

DEPARTMENT OF DEFENSE

32 CFR Part 219

DEPARTMENT OF EDUCATION

34 CFR Part 97

DEPARTMENT OF VETERANS AFFAIRS

38 CFR Part 16

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

NATIONAL SCIENCE FOUNDATION

45 CFR Part 690

DEPARTMENT OF TRANSPORTATION

49 CFR Part 11

Federal Policy for the Protection of Human Subjects

AGENCIES: United States Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Consumer Product Safety Commission; International Development Cooperation Agency, Agency for International Development; Department of Housing and Urban Development; Department of Justice; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; Department of Transportation.

ACTION: Final rule.

SUMMARY: This document sets forth a common Federal Policy for the Protection of Human Subjects (Model Policy) accepted by the Office of Science and Technology Policy and promulgated in regulation by each of the listed Departments and Agencies. A Proposed Federal Policy for the Protection of Human Subjects published November 10, 1988 (53 FR 45661) has been revised in response to public comments. The Policy as revised is now set forth as a common final rule. For related documents, see other sections of this **Federal Register** part.

EFFECTIVE DATE: These regulations shall become effective on August 19, 1991. The Department of Education regulations (34 CFR part 97) take effect either August 19, 1991, or later if Congress takes certain adjournments. If you want to know the effective date of the Department of Education regulations in 34 CFR part 97, call or write Mr. Edward Glassman, Office of Planning, Budget and Evaluation, U.S. Department of Education, room 3127, 400 Maryland Avenue SW., Washington, DC 20202-4132. A document announcing the effective date of the Department of Education regulations will be published in the **Federal Register**. Institutions currently conducting or supporting research in accord with Multiple Project Assurances of Compliance (MPAs)

approved by and on file in the Office for Protection from Research Risks (OPRR) in the Department of Health and Human Services may continue to do so in accord with the terms and conditions of their MPAs. See Supplementary Information for further details.

FOR FURTHER INFORMATION CONTACT: Dr. Joan P. Porter, (301) 496-7005. Office for Protection from Research Risks, National Institutes of Health, Building 31, room 5B59, Bethesda, MD 20892.

SUPPLEMENTARY INFORMATION: Paperwork Reduction Act Requirements: Sections _____103(a);

_____103(b); _____103(b)(4)(i);

_____103(b)(4)(iii);

_____103(b)(5); _____103(f);

_____109(d); _____113;

_____115(a); _____116; and

_____117 contain information collection requirements subject to approval by the Office of Management and Budget (OMB) under the Paperwork Reduction Act. HHS has submitted the request for approval to OMB on behalf of all Departments and Agencies governed by this final rule and has published elsewhere in this issue of the **Federal Register** a request for OMB expedited review and approval of the information collection requirements. OMB has assigned OMB control number 9999-0020; however, the information collection requirements will not become effective until OMB has approved them. Unless a notice is published to the contrary, the public may assume that OMB has approved the information collection requirements during the 60-day period before the final rule becomes effective.

For further information regarding OMB approval of the information collection, contact Ms. Shannah Koss-McCallum, OMB, (202) 395-7316.

Compliance Dates: Institutions that hold MPAs are permitted and encouraged to apply all provisions of this final rule as soon as it is feasible to do so. They are urged not to wait for the negotiation and approval of a revised MPA to begin to function in accord with this rule. The OPRR, acting on behalf of the Secretary, Department of Health and Human Services (HHS), will continue to renegotiate and approve MPAs in the normal periodic cycle of renewal.

Institutions that are not operating under an MPA approved by OPRR will be required to negotiate an Assurance of Compliance with the supporting Department or Agency, prior to initiating research involving human subjects.

Institutions with MPAs approved by and on file with HHS will be allowed a "grace period" of sixty days after the

submission date for an application seeking HHS support, to provide certification of Institutional Review Board (IRB) review and approval. Exceptions may occur for reasons of Congressional mandate or special program or review requirements. In such cases, institutions will be advised that certification must be sent at an earlier time.

Background

This notice sets forth as a common rule requirements for the protection of human subjects involved in research conducted or funded by the following Federal Departments and Agencies: United States Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Consumer Product Safety Commission; International Development Cooperation Agency; Agency for International Development; Department of Housing and Urban Development; Department of Justice; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; National Science Foundation; Department of Health and Human Services and the Department of Transportation. Each of these Departments and Agencies have adopted the common rule as regulations to be codified as listed above.

The Food and Drug Administration (FDA) Final Rule to modify current regulations to conform to the Federal Policy are presented elsewhere in this issue of the *Federal Register*. Existing FDA regulations governing the protection of human subjects share a common core with the Federal Policy and implement the fundamental principles embodied in that policy. The agency is committed to being as consistent with the final Federal Policy as it can be, given the unique requirements of the Federal Food, Drug, and Cosmetic Act under which FDA operates; and the fact that FDA is a regulatory agency that rarely supports or conducts research under its regulations.

Adoption of the common Policy by Federal Departments and Agencies in regulatory form will implement a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research which was established on November 9, 1978, by Public Law 95-622. One of the charges to the President's Commission was to report biennially to the President, the Congress, and appropriate Federal Departments and Agencies on the

protection of human subjects of biomedical and behavioral research. In carrying out that charge, the President's Commission was directed to conduct a review of the adequacy and uniformity (1) of the rules, policies, guidelines, and regulations of all Federal Departments and Agencies regarding the protection of human subjects of biomedical or behavioral research which such Departments and Agencies conduct or support, and (2) of the implementation of such rules, policies, guidelines, and regulations by such Departments and Agencies, such review to include appropriate recommendations for legislation and administrative action.

In December 1981 the President's Commission issued its First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research, Protecting Human Subjects.

In accord with Public Law 95-622, each Federal Department or Agency which receives recommendations from the President's Commission with respect to its rules, policies, guidelines or regulations, must publish the recommendations in the *Federal Register* and provide an opportunity for interested persons to submit written data, views and arguments with respect to adoption of the recommendations. On March 29, 1982 (47 FR 13262-13305), the Secretary, HHS, published the recommendation on behalf of all affected Departments and Agencies.

In May 1982 the Chairman of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET) appointed an *Ad Hoc* Committee for the Protection of Human Research Subjects under the auspices of the FCCSET. The Committee, chaired by Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Health and Human Services (HHS), was composed of representatives and ex-officio members of the affected Departments and Agencies. In consultation with the Office of Science and Technology Policy (OSTP) and the Office of Management and Budget, the *Ad Hoc* Committee, after considering all public comments, developed responses to the recommendations of the President's Commission. After further review and refinement, OSTP responded on behalf of all the affected Department and Agency Heads to the recommendations of the President's Commission, including the recommendation that:

The President should, through appropriate action, require that all federal departments and agencies adopt as a common core the

regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR Part 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions.

The *Ad Hoc* Committee agreed that uniformity is desirable among Departments and Agencies to eliminate unnecessary regulation and to promote increased understanding and ease of compliance by institutions that conduct federally supported or regulated research involving human subjects. Therefore, the *Ad Hoc* Committee developed a Model Federal Policy, which applies to research involving human subjects conducted, supported or regulated by Federal Departments and Agencies. In accordance with the Commission's recommendation, the Model Federal Policy is based on subpart A of the regulations of HHS for the protection of human research subjects (45 CFR part 46). The Proposed Model Federal Policy developed by the *Ad Hoc* Committee was modified by OSTP to enhance uniformity of implementation among the affected Federal Departments and Agencies and to provide consistency with other related policies. The revised Model Federal Policy was concurred in by all affected Federal Departments and Agencies in March 1985.

An Interagency Human Subjects Coordinating Committee was chartered in October 1983 under the auspices of FCCSET to provide continued interagency cooperation in human subject research once the *Ad Hoc* Committee had completed its assignment. It is chaired by the Director of the Office for Protection from Research Risks, HHS, and composed of representatives of all Federal Departments and Agencies that conduct, support or regulate research involving human subjects. The Committee is advisory to Department and Agency Heads and, among other responsibilities, will evaluate the implementation of the Federal Policy and recommend modification as necessary.

On June 3, 1986, OSTP published for public comment in the *Federal Register* (51 FR 20204) a Proposed Model Federal Policy for Protection of Human Subjects and Response to the First Biennial Report of the President's Commission. Over 200 written comments were received concerning the publication. The Interagency Human Subjects Coordinating Committee considered these comments in the revision of a common Federal Policy proposed as a common rule on November 10, 1988, for

adoption by each of the Departments and Agencies listed. Response to the more than 60 public comments, discussion of revisions made to that publication and the final common rule follow.

Summary of Public Comments
Received in Response to the November 10, 1988, **Federal Register** publication (53 FR 45661) of the Notice of Proposed Common Rulemaking, Federal Policy for the Protection of Human Subjects for 16 Federal Departments and Agencies.

In response to the November 10, 1988, publication, 66 commentators responded within the comment period, which was extended to February 8, 1989. The source of comments included institutional offices of sponsored research, departmental deans and chairs and other staff of academic institutions, institutional review board members and staff, principal investigators, and drug company representatives. Although there were 66 separate commentators, several responses were prepared by organizations each representing a consortium of institutions which had been polled concerning the notice of proposed common rulemaking. For example, the Council on Governmental Relations, the Association of American Medical Colleges, Public Responsibility for Medicine and Research, Association of American Universities, the American Medical Association and the Consortium of Social Science Associations offered comment on behalf of their member institutions.

In general, commentators endorsed the efforts of the Office of Science and Technology Policy and the Federal Departments and Agencies to develop a Common Rule for the protection of human subjects.

The majority of the comments dealt with three points in the proposed common rule, as follows:

Section _____103(b)(5) concerns those procedures set forth in Assurances of Compliance for research conducted or supported by a federal Department or Agency. As proposed, this section required that an Assurance should include:

Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head (i) any unanticipated problems or scientific misconduct involving risks to human subjects or others (ii) any instance of serious or continuous noncompliance with this policy or the requirements of determinations of the IRB and (iii) any suspension or termination of IRB approval.

Some commentators indicated that they believed the proposed policy would inappropriately require IRBs to notify Department and Agency heads of

scientific misconduct involving risks to human subjects and others and that the scientific fraud and misconduct regulations [September 19, 1988, Responsibilities of PHS Awardee and Applicant Institutions for Dealing with and Reporting Possible Misconduct in Science (53 FR 36344)] create duplicate and potentially conflicting requirements. Several suggested that the proposed rules on misconduct should leave undisturbed other existing regulatory schemes such as human subjects regulations of the Department of Health and Human Services at 45 CFR part 46. Other commentators indicated that the IRB should not have a "police" role and that its members are potentially legally liable if they did or did not report certain misconduct activities. Concern was also noted about additional responsibility and work placed on the IRB.

Several commentators requested clarification of § _____103(b)(5)(i) in the terms "misconduct" and "unanticipated" problems. Respondents suggested that scientific misconduct implies falsification of data, plagiarism, abuse of confidentiality, dishonesty in presenting publications, legal violations and a range of other activities which should be addressed in a separate policy involving broader institutional considerations than those appropriate for an IRB. In addition, some respondents suggested that actual "harm" rather than "possible risk" to human subjects be reported to Departments and Agencies.

Concerning § _____103(b)(5)(iii) two commentators suggested that IRBs would be reluctant to suspend IRB-approved research for administrative infractions (such as tardiness of response to an IRB) if such suspension must be reported to an Agency. One commentator requested that revisions be made so that only suspensions or terminations for serious or continuing noncompliance with the policy or determination of the IRB need be reported to the Department or Agency head. In that way, IRBs would use suspension or termination as an administrative tool and continue to keep Departments and Agencies informed of serious problems.

One specific set of comments addressed all aspects of this section by suggesting deletion of reporting requirements to Department and Agency Heads altogether. Rather, reports to IRBs and institutional officials would be required concerning unanticipated problems involving risks to human subjects which are substantial; proven scientific fraud; instances of substantial or continuing noncompliance with the

policy or the requirements or determination of the IRB; or any suspension or termination which is more than minor or temporary.

Response

In view of the comments and the policy concerning fraud and misconduct that is now under deliberation, the Interagency Human Subjects Coordinating Committee revised § _____103(b)(5) as follows:

Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

The President's Commission recommended in its 1981 *First Biennial Report* that institutional assurances should specify how "misconduct" should be reported and investigated (pp. 77-82, Recommendations 7 and 8). Since the time of the publication of the 1981 report, however, the issue of identification and reporting of misconduct has been deliberated in many other contexts and has included consideration of more than "misconduct involving risks to human subjects." In August 1989 the Department of Health and Human Services published a final rule announcing responsibilities of awardee and applicant institutions for dealing with and reporting possible misconduct in science [53 CFR 32446]. The Committee agrees that in the current context the inclusion of the term "misconduct" in the Federal Policy is confusing and misleading because other policy development efforts giving specific meaning to scientific misconduct are ongoing. Therefore, the term is deleted from this document.

The revised language is closer to that of the original provision in the Department of Health and Human Services regulations. The Interagency Committee wishes to clarify that it was never the intention of the Policy to require IRBs to report directly to Department and Agency Heads. Assurances of Compliance are negotiated between Departments or Agencies and awardee institutions. Assurances allow institutions to specify how reporting to Department and Agency Heads will take place. Reporting is the responsibility of the institutional official identified in each Assurance.

Further, the Committee wishes to clarify that "unanticipated problems" in this context includes serious and unexpected reactions to biologicals,

drugs, or medical devices. Institutions have flexibility to establish channels of reporting to meet reporting requirements of Departments and Agencies. In addition, the Committee believes it is important that suspension or termination, for whatever reason, be reported to the Department and Agency Heads.

The Sixty Day "Grace" Period

Comment

The section of the proposed Policy and Final Rule eliciting the most comments was 103(f) regarding submission of certification. That section is as follows:

Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §§ _____101 (b) or (i). An institution with an approved assurance shall certify research covered by the assurance and by § _____103 of this policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by § _____103 of the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

Most of the commentators (50) addressed the need for a grace period between the time of submission of an application for support to a Department and Agency and submission of certification by the IRB of review and approval of the proposal. A 60-day grace period was allowed in the previous Department of Health and Human Services Regulations for the Protection of Human Subjects. Under this provision, institutions with Multiple Project Assurances on file with HHS had sixty days to complete IRB review and approval and to notify HHS. This period of time roughly corresponded to the time between receipt of the application and initial scientific merit review. The groups evaluating the application for scientific merit need certification of the fact that an appropriate IRB has determined that human subject protections are adequate.

The commentators cited many reasons why a grace period is important for orderly institutional review and for protection of human subjects. Many of

the comments on this section requested that the grace period be reinstated in the regulations. In brief, respondents noted that if the grace period is not allowed, investigators would be required to submit proposals to IRBs about two months earlier than at present. IRBs would be convened into emergency sessions or required to meet more frequently. Pressure to grant approval would increase.

Some commentators noted that institutions that have no Multiple Project Assurance on file with HHS are given 30 days to review and certify upon HHS request. If Multiple Project Assurance holders have no grace period, they may be at a disadvantage in time permitted for preparation and institutional review of their applications as compared to the time permitted institutions without a Multiple Project Assurance. Also, data for competitive renewals is often added just before submission to HHS so that the most current progress under the original award can be reported. If a grace period is not offered, applications may not contain information vital for appropriate peer review.

Another concern raised was that some researchers are required to modify their proposals several times before submission. The current 60-day period allows the IRB to review the final submission carefully.

One commentator indicated that the proposed provision was acceptable to the institution.

Response

Many Federal Departments and Agencies do not have application review schedules that correspond to those of HHS. A 60-day grace period is without relevance to their review systems. At the time of publication of the proposed common rule, the Interagency Committee noted that HHS intended to retain a "grace period" for institutions that have Multiple Project Assurances and announce the period through advisories that are routinely received by institutions. HHS has carefully considered the public comments and will ordinarily retain the 60-day grace period in its administrative procedures. In some programs, such as AIDS-related research, HHS has modified the receipt and review schedules in accordance with a Congressional mandate.

The Departments and Agencies, other than HHS, adopting the common rule are aware of the concerns of the institutions and will provide as much flexibility to IRBs as possible in the orderly processing of applications for support. To require a 60-day grace period or any standard grace period for

all Departments and Agencies would require far-reaching changes in the review and processing systems of these organizations. Institutions will be advised of Department and Agency procedures through routine publications. Consequently, the language in the final rule remains unchanged.

Composition of the IRB

Comments

Section _____107 of the Policy deals with composition of the IRB. Several points made by commentators are as follows:

In § _____107(a) there is the requirement that if an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. The HHS regulations at 45 CFR part 46 promulgated in 1981 utilized a different standard, i.e., "if an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other subparts of [45 CFR part 46], the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects." The commentator indicated that his institution would retain previous standards, because advocates for special populations have been of great benefit in the IRB's decision-making process.

Another commentator wrote that in her institution, full committee review is required when a vulnerable population is involved; all committee members are advocates for subjects whether or not they themselves are involved in a vulnerable population. Adding new members would make the committee too large to be workable, she wrote.

The majority of the comments on this section were directed to the departure proposed by the Department of Education at 34 CFR part 97.107(a). The proposed departure was based on a concern for protection of mentally disabled persons and handicapped children. The departure would have provided that, for research conducted or supported by the Department of Education, "when an IRB reviews research that deals with handicapped children or mentally disabled persons, the IRB shall include at least one person primarily concerned with the welfare of the research subject." The remainder of the departure reiterated the common

rule's provision which required institutions to consider representation on the IRB of persons who are knowledgeable about and experienced in working with certain vulnerable subjects if the IRB regularly reviews research involving those vulnerable subjects. Twenty-one institutions commented on this proposed departure. The majority of these comments were opposed to the proposed departure.

Some commentators, while supporting the proposed language in § _____,107, stated their belief that the departure was not necessary because the policy in § _____,107 already addresses representation of the special concerns of vulnerable subjects on the IRB. Thus, the rights of handicapped children and mentally disabled persons should be represented on any IRB that regularly reviews proposals involving those individuals, and there is no constructive advantage to emphasizing these two categories of subjects. Such an emphasis was seen as a precedent with the potential for discrimination against other categories of vulnerable subjects. When special expertise is required, IRBs already have the option and the obligation to seek informed consultants, respondents noted. One commentator stated, however, "If in future staffing of our IRB, someone with expertise in this area is available and willing to serve, we would be happy to encourage such participation."

Some commentators objected to the lack of consistency among Federal Departments and Agencies and cited the Department of Education's proposed departure as being inconsistent with the purpose of the common rule.

One commentator suggested that only when the IRB regularly reviews research that deals with handicapped children or mentally disabled persons should the IRB include at least one person primarily concerned with the welfare of the research subjects. Otherwise, consultation should take place when appropriate. Another suggestion was that handicapped children and mentally disabled persons be added to the list of examples of vulnerable subjects for which an IRB that regularly reviews research might want to consider inclusion of one or more members who are knowledgeable about and experienced in working with these subjects.

Response

The Department of Education has considered these comments carefully and has decided to withdraw the departure to the common rule and to adopt the common rule as promulgated in this document. The Secretary,

however, continues to believe that there is a special need to protect handicapped children and mentally disabled persons. Thus, the Secretary strongly urges institutions to include at least one person who is primarily concerned with the welfare of the research subjects whenever the research involved handicapped children or mentally disabled persons. While the Secretary agrees to the common rule provision regarding IRB representation as a general matter, the Secretary has decided to address the concerns underlined by the proposed departure on a programmatic basis under the Department of Education's programs of the National Institute on Disability and Rehabilitation Research (34 CFR parts 350 and 356). Accordingly, the Secretary amends the program regulations for these programs in a document published in another section of this **Federal Register** part.

In light of the concern of the Department of Education that these groups were not clearly identified as vulnerable populations, "handicapped" has been added to the illustrative list in § _____,107.

Comments on Other Sections

Section _____,101 explains the application of the Policy. Section _____,101(b) describes categories of research that are exempt from the Policy.

Comment

Several commentators indicated that the language and intent of this section was helpful. One commentator indicated that he believes the section was written primarily for medical and health research and should not apply to involvement of human subjects for general business interviews or surveys. The commentators recommended the exemption of information gathering related to business. Further comment suggested that all minimal risk research be exempt from the regulations.

Response

The Committee believes that the exemptions are sufficiently clear so that all types of research, not just biomedical or health research, may be reviewed using the specified criteria. In addition, the Committee has indicated that the exemptions of § _____,101(b) of the Policy provides for the exemption of certain research including much of the research used by business (e.g., survey research) in which there is little or no risk.

Section _____,101(b)(2)

Comment

Section _____,101(b)(2) is an exemption for research involving the use of educational tests, survey procedures or observation of public behavior. To paraphrase, this type of research is exempt unless information is recorded in a manner such that subjects can be identified and disclosure of the responses outside the research could place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. Three commentators expressed concern that the additional subparts B, C, and D of the HHS regulations for the protection of human subjects are not part of the Federal policy. They noted that institutions with assurances with HHS will be required to apply provisions of those subparts in research they support or conduct, while other Federally-supported research would not be subject to the subpart requirements.

Others commenting on § _____,101(b)(2) indicated that research that could involve sensitive data could place the subjects at risk, even if information is not recorded in such a manner that human subjects can be identified and should not be exempt from provisions of the Policy. One respondent noted that one IRB reviews this type of research even if an exemption is permitted by the regulations. Another indicated that this section will exclude from normally exempt educational, survey, interview or observational research any instances wherein disclosure of subjects responses could be damaging to the subject's reputation. Because reputation is a subjective term that is difficult to define operationally, the commentator suggested that the wording be changed to limit exceptions to specific risks of "professional and sociological damage."

Response

The Interagency Committee may at a later date wish to consider incorporation or provisions of the other subparts of the HHS regulations into federal policy. However, such considerations should not delay publication of basic protections for all human subjects. At this time, institutions sponsoring research under HHS-approved assurances will adhere to provisions of all the subparts of 45 CFR part 46. A footnote has been added to § _____,101(b) indicating that

Institutions with HHS-approved assurances on file will abide by provisions of 45 CFR 46 subparts A-D. Some of the other

Departments and Agencies have incorporated all provisions of 45 CFR 46.101(b) into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

A Notice to amend subpart D, 45 CFR 46.401(a)(2)(b) to renumber exemptions to permitted and not permitted to conform the subpart D reference to the renumbered exemptions in the Common Rule is published elsewhere in this issue of the **Federal Register**.

Under this footnote, for research involving children, institutions that have Multiple Project Assurances on file with OPRR will not be able to use all provisions in the exemption in § _____.101(b)(2). However, the educational tests basis for the exemption contained in § _____.101(b)(2) will still be available to institutions conducting research involving children. In developing the common rule, a number of HHS exemptions were consolidated, including the HHS educational tests exemption. The educational tests exemption has been available for use under subpart D of the HHS regulations, Additional Protections Involving Children. Thus, the footnote to the common rule continues the provision that existed under the previous regulations.

Some institutions do not choose to permit exemptions even if they are permitted by the policy. This is their prerogative, and assurances of compliance incorporate provisions for utilizing exemptions.

Section _____.101(b)(3)

Comment

Section _____.101(b)(3) described an exemption for research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior that is not exempt under the exemption in § _____.101(b)(2) if human subjects are elected or appointed public officials or candidates for public office or if Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. Two commentators recommended deletion of this exemption because confidentiality considerations

are not the only purpose of IRB review. Other human subjects protections issues might need to be considered in research that is not exempt by the criteria described in § _____.101(b)(2).

Furthermore, the commentators explained that IRBs and institutions will not know that Federal statutes afford these protections, and inconsistency and confusion is likely.

Response

At present the only statutes that meet the criteria in § _____.101(b)(3)(ii) of which the Committee is aware are those for research conducted or supported by the Department of Justice under 42 U.S.C. 3789g, and certain research conducted or supported by the National Center for Education Statistics of the Department of Education under 20 U.S.C. 1221e-1. The Department of Justice's Office of Justice Programs (OJP) has several constituent offices that conduct research that would fall under § _____.101(b)(3). The law governing OJP research activities, 42 U.S.C. 3789g(a), provides that

Except as provided by Federal law other than this chapter, no officer or employee of the Federal Government, and no recipient of assistance under the provisions of this chapter shall use or reveal any research or statistical information furnished under this chapter by any person and identifiable to any specific private person for any purpose other than the purpose for which it was obtained in accordance with this chapter. Such information and copies thereof shall be immune from legal process, and shall not, without the consent of the person furnishing such information, be admitted as evidence or used for any purpose in any action, suit, or other judicial, legislative, or administrative proceedings.

The law governing research conducted by the National Center for Education Statistics under 20 U.S.C. 1221e-1 provides that data collected by the National Center for Education Statistics may not be used for any purpose other than the statistical purpose for which the data were collected and establishes further protections regarding that data, including a provision that they

shall be immune from legal process, and shall not, without the consent of the individual concerned, be admitted as evidence or used for any purpose in any action, suit, or other judicial or administrative proceeding. 20 U.S.C. 1221e-1(d)(4)(B).

It is the responsibility of a Federal Department or Agency to assist the institutions proposing to conduct a research project which it supports in determining if the research is subject to the provisions of the Federal statutes

meeting the criteria in § _____.101(b)(3)(ii).

Section _____.101(h)

Comment

Section _____.101(h) discusses research that takes place in foreign countries covered by the policy. One respondent endorsed this section. Another found the provision somewhat ambiguous and suggested that it be made clear that a researcher may either comply with the policy provision or may substitute the foreign procedure in lieu of the policy only following a determination by the Department or Agency Head that the foreign procedures are at least equivalent to those required in the policy. Another comment reflected that it may be difficult at the time of submitting a research proposal to a supporting Department or Agency to know if a foreign country's guidelines provide protections which are at least equivalent to the policy; the Interagency Committee or Department or Agency Heads should publish regulations or advisories indicating which are considered "equivalent."

Response

The Interagency Committee concurs that evaluation of other country's protection requirements in comparison with the policy will be an important Committee initiative and it will consider publication of notices that reflect the decisions of Department and Agency Heads.

Also in § _____.101(h), reference to Helsinki as amended in 1983 is now changed to Helsinki as amended in 1989.

Section _____.102 Definitions

Comment

Section _____.102 includes the definition section in the Federal Policy. In this section, one commentator asked for a definition of "principal investigator," since that individual bears responsibility for human subject protection. Another commentator suggested adding a definition of "scientific fraud."

Another suggestion was to take into account First Amendment concerns involving freedom of speech in situations where social scientists interview foreign and domestic government and private individuals to obtain information. Another commentator suggested that the definition of human subject in § _____.102(f) should make clear that with respect to interview research, a distinction should be made between

information provided by a person which relates to past or present events or the actions of others, as opposed to the attitudes or actions of the interviewees themselves; only in the latter case should the interviewee constitute a human subject. Also, another letter explained that in some cultures, ancestral research would not come under the definition of "human subject" because individuals were deceased. However, this type of research might be distressing to living family members.

Section _____.102(b) includes the definition of "institution." One commentator proposed that the definition of "private entity" should also be included.

Section _____.102(h) includes the definition of "IRB approval." Three commentators suggested that the term "at the institution" was not appropriate in the definition of approval as " * * * determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements." Much of the research of an institution is off-site and thus seemed to be in technical violation under the proposed language.

Response

The Interagency Committee agrees that the principal investigator is a key person for protection of human subjects and bears a broad responsibility for implementation of the requirements. The term "investigator" is used in the policy, but not "principal investigator" and no definition is provided because the responsibility for protecting human subjects is shared by the entire research team. No definition of scientific fraud has been included, and the term has been deleted from § _____.103(b)(5), as described previously.

The Committee believes that the comment on § _____.102(f), definition of "human subject," about interview content is addressed through application of exemption criteria in § _____.101(b)(2) as well as in the precise wording of the definition itself.

In response to the comments about the phrase "at the institution" in the definition of IRB approval in § _____.102(h), the Interagency Committee responds that there are instances in which the IRB has approval authority where the research is not conducted at the institutional site. The policy at § _____.114, Cooperative Research, is an important cross-reference.

Establishment and approval of other off-site IRBs may be required in some circumstances in which another

institution is involved in research. The Department or Agency Heads reserve the authority to approve cooperative arrangements. The phrase "at the institution" in the definition of IRB approval should be interpreted to mean field sites and other off-site facilities over which an institution has jurisdiction.

Section _____.103 Assurances

Comment

Section _____.103 explains how compliance is assured under this Policy in research conducted or supported by a federal Department or Agency. Most of the comments on this section concerned reporting and misconduct issues in § _____.103(b)(5) or the "grace period" or timing of certification in § _____.103(f), discussed previously. Several other comments are as follows: Three respondents asked for clarification of the rationale for reporting requirements in § _____.103(a). This section requires that when the existence of an HHS-approved assurance is accepted in lieu of requiring submission of a new assurance, reports required by the Policy are to be made to the Department and Agency Heads. Reports (with the exception of certification) are also to be made to OPRR.

Another comment was prompted by review of § _____.103(b)(1) which requires inclusion in the assurance of principles governing the institution in protection of human subjects, such as a statement of ethical principles or existing codes. The commentator suggested that a statement as to the purpose of having regulations which create an IRB structure should be explicitly included in the regulations.

A comment concerning § _____.103(f) requests clarification on what type of certification documentation will be acceptable.

Response

In consideration of these comments, the Interagency Committee offers the following information. In § _____.103(a) the only reports required to be made to both the head of the Department or Agency supporting the research and the OPRR when the HHS assurance is utilized are those required under § _____.103(b)(5). The head of the Department or Agency supporting a research project must have information concerning conduct of that research including instances of unanticipated problems or serious or continuing noncompliance with the Policy or the requirements or determinations of the IRB and any

suspension or termination of IRB approval. OPRR requires this information to ensure that human subjects protections under the Policy and under the HHS-approved Assurance are being properly implemented and that institutions have fulfilled their requirements in an appropriate and timely manner.

With regard to the comment concerning certification requirements in § _____.103(f), standardized language for the certification will be developed. Certification now used by HHS has been suggested as a basis for development of the language.

Section _____.107 IRB Membership

Comment

Most of the commentators on § _____.107 address the proposed departure on IRB membership for the Department of Education that has been discussed above [§ _____.107(a)]. Other comments received were as follows: Reference is made in the Policy in several places to vulnerable subject populations. One commentator indicated that all subject populations are vulnerable and that the term "exceptionally vulnerable" would be better phraseology for those instances for which additional safeguards are urged or required.

Section _____.107(b) requires that every reasonable nondiscriminatory effort be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes. One respondent indicated that the HHS standard in the regulations published in 1981 requiring that no IRB shall be constituted entirely of men or entirely of women should be retained. A further requirement of § _____.107(b) is that no IRB may consist entirely of members of one profession. Another respondent suggested that the word "discipline" be substituted for "profession."

Response

The Committee did not believe that the suggested language changes would significantly improve the understanding or implementation of the sections. It expects that institutions will use good judgment and diligence in selecting persons as IRB members who can fulfill the requirements of § _____.107 (a) and (b) so that persons of both genders and persons with varying backgrounds will promote responsible review of the research activities. In approving Assurances, the Federal Departments and Agencies that conduct, support or regulate research will review IRB

composition to ensure that the membership is appropriate for the research, and may request that membership be supplemented if complete and adequate review of the research does not appear possible.

As regards the gender consideration in IRB composition the Committee notes that in seeking diverse membership on the IRB, the institution must consider both men and women who can contribute to the role of the IRB.

Section _____ .110 Expedited Review Procedures

Comment

This section sets forth expedited review procedures for certain kinds of research involving no more than minimal risk and for minor changes in approved research. Section _____ .110(b) indicates that an IRB may use the expedited review procedure under certain specified circumstances with the approval of Department or Agency heads. Four respondents noted that confusion may result in institutions if Departments or Agencies have different requirements. Furthermore, it may be burdensome to IRBs and institutions to seek Department and Agency approval for use of expedited review. One respondent recommended that the phrase "with the approval of department or agency heads" in § _____ .110(b) be deleted because it will result in bureaucratic delays in approval to use the authority. Furthermore, the authority to restrict use of expedited review is found in § _____ .110(d) whereby the Department or Agency head may restrict, suspend, terminate or choose not to authorize the use of the expedited review procedure.

Response

The Committee agreed that the phrase in § _____ .110(b) "with the approval of department or agency heads," should be deleted because § _____ .110(d) accomplished the intention of the Committee. As an example of Department and Agency use of this authority, note that HHS does not permit expedited review for institutions that do not hold Multiple Project Assurances of Compliance. Note also that some institutions which have authority to use expedited procedures choose to use full IRB review instead.

Note that parentheses have been added to the word "reviewer(s)" in § _____ .110(b)(1) to clarify that one or more reviewers may carry out the expedited review procedures in accordance with § _____ .110(b).

Section _____ .111 Criteria for IRB Approval of Research

Comment

Three commentators requested deletion of the term "economically or educationally disadvantaged" in the examples of those who are vulnerable subjects because of lack of clarity of the term, difficulty in determining if some subjects were in this category and possible exclusion from beneficial research protocols of those deemed to be included in this category.

Response

The Committee believes that the criteria for participation and the potential vulnerability of some research subjects are still a very important consideration for IRBs. In exercising their responsibilities, IRBs are charged with evaluating the benefits and the burdens of the research so that unjust social patterns do not appear in the overall distribution of the burdens and benefits of research. The 1979 Belmont Report outlining ethical principles and guidelines for the protection of human subjects of research written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research makes special note that some populations are burdened in many ways by their social circumstances and environments.

* * * when research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called on first to accept these risks of research, except where research is directly related to the specific conditions of the class involved.

* * * certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

The Committee expects that in its review of equitable treatment and review of benefits and burdens, the educationally or economically disadvantaged will not be excluded from potentially beneficial research to individuals or to those persons as a class.

Section _____ .113 Suspension or Termination of IRB Approval of Research

Comment

One comment was offered suggesting that institutions, not IRBs, should report to Department and Agency Heads. Another response recommended that OPRR be designated as the central coordinating office to which such notification should be sent. Designation of OPRR as the single reporting channel would ensure prompt requisite reporting to the Government, the commentator noted.

Response

This section does not require that the IRB report to the Department or Agency head. The responsibility for reporting is specified in the institution's assurance.

OPRR will receive reports if institutions have an assurance on file with the HHS which covers the research in question and will be notified in accordance with § _____ .103(b)(3). OPRR cannot act as a central information office for other Departments and Agencies in receiving reports of this nature because of insufficient resources and regulatory jurisdictional considerations.

Section _____ .114 Cooperative Research

Comment

Confusion may result for institutions if Departments and Agencies have differing requirements.

Response

The Committee will attempt to advise Departments and Agencies so that procedural requirements will be consistent.

Section _____ .115 IRB Records

Comment

Modified language for this section was suggested to assure that confidentiality will be maintained to the greatest extent possible.

Response

The Committee agreed that confidentiality considerations are most important for IRB records. While it rejected the detailed language suggested by the commentator, it acknowledged the importance of maintaining confidentiality. It believes that the proposed language is adequate.

Section _____ *116 General Requirements for Informed Consent; and*

Section _____ *117 Documentation of Informed Consent*

Comment

One respondent wrote that the differences between § _____ .116 (c) and (d) and § _____ .117(c) were confusing.

Response

Section _____ .116(c) specifies that an IRB may approve a consent procedure which alters some or all of the required elements of informed consent or waives the requirement to obtain informed consent in research or demonstration projects which are subject to approval of state and local authorities and which meet certain other requirements. Section _____ .116(d) specifies that an IRB may, under limited circumstances [other than those of § _____ .116(c)] approve a consent procedure which alters some or all of the elements of informed consent or waive the requirements to obtain informed consent for certain types of research. Section _____ .117(c) specifies conditions under which an IRB may waive the requirement for the investigator to obtain a signed consent document for some or all subjects in the research.

Section _____ *123 Early Termination of Research*

Comment

Two commentators expressed concern the establishment of this section implies that a "blacklist" composed of individuals and institutions that, in the judgment of Department and Agency Heads, have failed to discharge properly their responsibilities for the protection of human subjects. Serious breaches of confidentiality and due process could be implied. The inclusion of the parenthetical phrase "(whether or not the research was subject to federal regulations)" was also of concern because it implies that information gathering may lead to violations of confidentiality.

Response

The Committee is aware of concerns about the need for confidentiality and due process considerations. The Committee notes that other federal regulations deal with the suspension and termination of funding. These regulations provide the requisite due process. Sources of information and criteria to be used by Department and Agency Heads for making decisions are

addressed with more specificity in those regulations. The federal government does maintain information that is pertinent to the exercise of the discretionary authority to award funding. Appropriate confidentiality protections apply to that information.

Section _____ *124 Conditions*

Comment

A suggestion was made that additional considerations of the Department or Agency head noted in this section should be limited to those required by statute.

Response

The Committee, in its ongoing deliberations, will attempt to maintain consistency and minimize burdens to institutions.

Department and Agency—Specific Comments

Department of Education

The 34 CFR 97.107(a) departure on composition of the IRB was discussed earlier in this preamble.

The Department of Education proposed to amend § _____ .101(b)(3). To what does this policy apply, by revising paragraph (b)(3)(ii) to exempt educational tests and surveys, interviews, or certain observations from coverage of the regulations if the research is conducted under a program subject to the protections of the General Education Provisions Act (GEPA). This departure would have expanded upon an exception contained in the common rule that exempted research conducted under a statute that requires that the confidentiality of the personally identifiable information be maintained, without exception, throughout the research and thereafter.

Much of the research that would have been covered by the GEPA exception is conducted by the National Center for Education Statistics (NCES). Since publication of the NPRM for the common rule, the Department has developed procedures implementing new authority under GEPA that establish absolute confidentiality for individuals who are the subjects of the NCES research which is subject to the confidentiality requirements of section 406(d)(4) of GEPA. Thus, NCES research covered by the GEPA confidentiality requirements now falls within the exception in the common rule that excludes from coverage of the regulations research under a statute that provides for absolute confidentiality [§ _____ .101(b)(3)(ii)] and an

expanded exception for that research is unnecessary.

The Secretary has decided to withdraw the GEPA departure as being inconsistent with the Department's overall objective of ensuring that research conducted or sponsored by the Department contain the greatest possible protections consistent with the common rule. Research of the Department other than that conducted under the NCES statute will be covered by the common rule.

Comment

Four comments were received regarding the exception from the common rule requirements for programs covered by GEPA. Three of the commentators were concerned that the proposed departure removed safeguards or did not provide additional safeguards for the protection of research subjects, while possibly increasing administrative burden on IRBs. One of these three commentators was concerned that the proposed departure might prohibit certain research procedures as applied to educational practices or programs. One commentator indicated that the proposed departure would not pose any problems.

Response

The departure to § _____ .101(b)(3)(ii) was based on statutes applicable to the Department that provide protection for subjects of the Department's education-related tests and surveys, interview procedures, and observation of public behavior. The protections are found in the GEPA at section 400A (control of paperwork) (20 U.S.C. 1221-3); section 406(d)(4) (confidentiality of National Center for Education Statistics data) (20 U.S.C. 1221e-1); section 438 (Family Educational Rights and Privacy Act) (20 U.S.C. 1232g); and section 439 (Protection of Pupil Rights Amendment) (20 U.S.C. 1232h). The departure was not intended to create additional burdens for IRBs but to eliminate the need for IRB approval of research in those cases where the research was subject to the GEPA. The Secretary has withdrawn the proposed departure because it is inconsistent with ensuring the greatest protection under the programs administered by the Department.

Because the departure is being withdrawn, there is no need to explain how the proposed departure would have affected research practices.

Department of Veterans Affairs (VA)

Concern was expressed that § _____ .111(a)(4) and § _____ .116 of

the Federal Policy would supersede the Veterans Administration Department of Medicine and Surgery (VA DM&S) Circular 10-88-50 which allows next of kin to grant consent for incompetent relatives under specific conditions.

The VA responded, however, that Federal Policy mandates informed consent by the subject, or the subject's "legally authorized representative." "Legally authorized representative" is defined to include "individual(s) * * * authorized under applicable law * * * to consent on behalf of a prospective subject * * *." Thus, the proposed consent does not preclude next of kin consent so long as such consent is "authorized under applicable law."

38 U.S.C. 4131, and VA policies promulgated thereunder, do authorize next of kin consent. Accordingly, the Common Federal Policy and current VA policies are consistent.

Department of Justice

The Department of Justice intends to retain special protections for prison populations in research it supports or conducts in accordance with 28 CFR parts 22 and 512.

Department of Defense

Comment

One response requested clarification of how the Federal Policy will extend to DOD research. Numerous questions concerning applicability to military and non-military personnel, voluntary versus mandated participation situations, identifiable data and the broad range of DOD-sponsored research were posed. The respondent indicated that formulating guidelines for informed consent is particularly important in the military context.

Response

Questions raised regarding application of the proposed regulations to DOD-supported research are reasonable and appropriate but are regarded as agency specific. DOD plans to address these particular issues through revision of DOD Directive 32-16.2, Protection of Human Subjects in DOD-supported Research.

The text of the common rule is adopted by the following Department and Agencies as set forth below:

Text of the Common Rule

The text of the Common Rule as adopted by the Department and Agencies in this document appears below:

CFR Part _____—Protection of Human Subjects

- Sec. _____101 To what does this policy apply?
- _____102 Definitions.
- _____103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- _____104—_____106 [Reserved]
- _____107 IRB Membership.
- _____108 IRB functions and operations.
- _____109 IRB review of research.
- _____110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- _____111 Criteria for IRB approval of research.
- _____112 Review by institution.
- _____113 Suspension or termination of IRB approval of research.
- _____114 Cooperative research.
- _____115 IRB records.
- _____116 General requirements for informed consent.
- _____117 Documentation of informed consent.
- _____118 Applications and proposals lacking definite plans for involvement of human subjects.
- _____119 Research undertaken without the intention of involving human subjects.
- _____120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- _____121 [Reserved]
- _____122 Use of Federal funds.
- _____123 Early termination of research support: Evaluation of applications and proposals.
- _____124 Conditions.

§ _____101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in § _____102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in § _____102(e) must be reviewed and approved, in compliance

with § _____101, § _____102, and § _____107 through § _____117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the

procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the **Federal Register** or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the **Federal Register** or in such other manner as provided in department or agency procedures.¹

§ 102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

¹ Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR part 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR part 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of

routine physical or psychological examinations or tests.

(j) *Certification* means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§ ____ .103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under § ____ .101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with § ____ .103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the

department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under § ____ .101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by § ____ .103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by § ____ .103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ ____ .104 [Reserved]

§ ____ .105 [Reserved]

§ ____ .106 [Reserved]

§ ____ .107 IRB Membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly

conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ ____ 108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in

§ ____103(b)(4) and, to the extent required by, § ____103(b)(5).

(b) Except when an expedited review procedure is used (see § ____110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ ____109 IRB Review of Research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § ____116. The IRB may require that information, in addition to that specifically mentioned in § ____116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § ____117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ ____110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication

by the Secretary, HHS, in the **Federal Register**. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § ____108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§ ____111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the

possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § _____.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § _____.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ _____.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ _____.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ _____.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§ _____.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in § _____.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in § _____.103(b)(4) and § _____.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by § _____.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ _____.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research

covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will

involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ ____ .117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § ____ .116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A short form written consent document stating that the elements of informed consent required by § ____ .116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§ ____ .118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under § ____ .101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§ ____ .119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency,

and final approval given to the proposed change by the department or agency.

§ ____120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ ____121 [Reserved]

§ ____122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§ ____123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects

(whether or not the research was subject to federal regulation).

§ ____124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

DEPARTMENT OF AGRICULTURE

7 CFR Part 1c

RIN 0518-AA00

List of Subjects in 7 CFR Part 1c

Human subjects, Research, Reporting and record keeping requirements. Title 7 of the Code of Federal Regulations is amended by adding part 1c as set forth at the end of this document.¹

PART 1c PROTECTION OF HUMAN SUBJECTS

Sec.

- 1c.101 To what does this policy apply?
- 1c.102 Definitions.
- 1c.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 1c.104 [Reserved]
- 1c.105 [Reserved]
- 1c.106 [Reserved]
- 1c.107 IRB Membership.
- 1c.108 IRB functions and operations.
- 1c.109 IRB review of research.
- 1c.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 1c.111 Criteria for IRB approval of research.
- 1c.112 Review by institution.
- 1c.113 Suspension or termination of IRB approval of research.
- 1c.114 Cooperative research.
- 1c.115 IRB records.
- 1c.116 General requirements for informed consent.
- 1c.117 Documentation of informed consent.
- 1c.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 1c.119 Research undertaken without the intention of involving human subjects.
- 1c.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 1c.121 [Reserved]
- 1c.122 Use of Federal funds.
- 1c.123 Early termination of research support: Evaluation of applications and proposals.

¹See Footnote 1 on page 28023.

1c.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: December 13, 1990.

Charles E. Hess,

Assistant Secretary, Science & Education.

DEPARTMENT OF ENERGY

10 CFR Part 745

RIN 1901-AA13

List of Subjects in 10 CFR Part 745

Human subjects, Research, reporting, and Record-keeping requirements. Title 10 of the Code of Federal Regulations is amended by revising part 745 as set forth at the end of this document.¹

PART 745 PROTECTION OF HUMAN SUBJECTS

Sec.

- 745.101 To what does this policy apply?
- 745.102 Definitions.
- 745.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 745.104 [Reserved]
- 745.105 [Reserved]
- 745.106 [Reserved]
- 745.107 IRB Membership.
- 745.108 IRB functions and operations.
- 745.109 IRB review of research.
- 745.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 745.111 Criteria for IRB approval of research.
- 745.112 Review by institution.
- 745.113 Suspension or termination of IRB approval of research.
- 745.114 Cooperating research.
- 745.115 IRB records.
- 745.116 General requirements for informed consent.
- 745.117 Documentation of informed consent.
- 745.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 745.119 Research undertaken without the intention of involving human subjects.
- 745.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 745.121 [Reserved]
- 745.122 Use of Federal funds.
- 745.123 Early termination of research support: Evaluation of applications and proposals.
- 745.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 7254; 42 U.S.C. 300v-1(b).

Dated: December 21, 1990.

James D. Watkins,
Secretary of Energy.

**NATIONAL AERONAUTICS AND
SPACE ADMINISTRATION**

14 CFR Part 1230

RIN 2700-AA76

List of Subjects in 14 CFR Part 1230

Human subjects, Research, Reporting and Record-keeping requirements. Title 14 of the Code of Federal Regulations is amended by adding part 1230 as set forth at the end of this document.¹

**PART 1230 PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 1230.101 To what does this policy apply?
- 1230.102 Definitions.
- 1230.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 1230.104 [Reserved]
- 1230.105 [Reserved]
- 1230.106 [Reserved]
- 1230.107 IRB Membership.
- 1230.108 IRB functions and operations.
- 1230.109 IRB review of research.
- 1230.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 1230.111 Criteria for IRB approval of research.
- 1230.112 Review by institution.
- 1230.113 Suspension or termination of IRB approval of research.
- 1230.114 Cooperative research.
- 1230.115 IRB records.
- 1230.116 General requirements for informed consent.
- 1230.117 Documentation of informed consent.
- 1230.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 1230.119 Research undertaken without the intention of involving human subjects.
- 1230.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 1230.121 [Reserved]
- 1230.122 Use of Federal funds.
- 1230.123 Early termination of research support: Evaluation of applications and proposals.
- 1230.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

¹See Footnote 1 on page 28023.

Dated: December 20, 1990.

Richard H. Truly
Administrator.

DEPARTMENT OF COMMERCE

15 CFR Part 27

RIN 0690-AA17

List of Subjects in 15 CFR Part 27

Human subjects, Research, Reporting and recordkeeping requirements. Title 15 of the Code of Federal Regulations is amended by adding part 27 as set forth at the end of this document.¹

**PART 27 PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 27.101 To what does this policy apply?
- 27.102 Definitions.
- 27.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 27.104 [Reserved]
- 27.105 [Reserved]
- 27.106 [Reserved]
- 27.107 IRB Membership.
- 27.108 IRB functions and operations.
- 27.109 IRB review of research.
- 27.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 27.111 Criteria for IRB approval of research.
- 27.112 Review by institution.
- 27.113 Suspension or termination of IRB approval of research.
- 27.114 Cooperative research.
- 27.115 IRB records.
- 27.116 General requirements for informed consent.
- 27.117 Documentation of informed consent.
- 27.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 27.119 Research undertaken without the intention of involving human subjects.
- 27.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 27.121 [Reserved]
- 27.122 Use of Federal funds.
- 27.123 Early termination of research support: Evaluation of applications and proposals.
- 27.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: December 21, 1990.

Robert Mosbacher,
Secretary of Commerce.

**CONSUMER PRODUCT SAFETY
COMMISSION**

16 CFR Part 1028

RIN 3041-AA95

List of Subjects in 16 CFR Part 1028

Human subjects, Research, Reporting and recordkeeping requirements. Title 16 of the Code of Federal Regulations is amended by revising part 1028 as set forth at the end of this document.¹

**PART 1028 PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 1028.101 To what does this policy apply?
- 1028.102 Definitions.
- 1028.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 1028.104 [Reserved]
- 1028.105 [Reserved]
- 1028.106 [Reserved]
- 1028.107 IRB Membership.
- 1028.108 IRB functions and operations.
- 1028.109 IRB review of research.
- 1028.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 1028.111 Criteria for IRB approval of research.
- 1028.112 Review by institution.
- 1028.113 Suspension or termination of IRB approval of research.
- 1028.114 Cooperative research.
- 1028.115 IRB records.
- 1028.116 General requirements for informed consent.
- 1028.117 Documentation of informed consent.
- 1028.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 1028.119 Research undertaken without the intention of involving human subjects.
- 1028.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 1028.121 [Reserved]
- 1028.122 Use of Federal funds.
- 1028.123 Early termination of research support: Evaluation of applications and proposals.
- 1028.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: January 11, 1991.

Sheldon D. Butts,
Acting Secretary.

**INTERNATIONAL DEVELOPMENT
COOPERATION AGENCY, AGENCY
FOR INTERNATIONAL DEVELOPMENT**

22 CFR Part 225

RIN 0412-AA17

List of Subjects in 22 CFR Part 225

Human subjects, Research, Reporting and record-keeping requirements. Title 22 of the Code of Federal Regulations is amended by adding part 225 at set forth at the end of this document.¹

**PART 225 PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 225.101 To what does this policy apply?
- 225.102 Definitions.
- 225.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 225.104 [Reserved]
- 225.105 [Reserved]
- 225.106 [Reserved]
- 225.107 IRB Membership.
- 225.108 IRB functions and operations.
- 225.109 IRB review of research.
- 225.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 225.111 Criteria for IRB approval of research.
- 225.112 Review by institution.
- 225.113 Suspension or termination of IRB approval of research.
- 225.114 Cooperative research.
- 225.115 IRB records.
- 225.116 General requirements for informed consent.
- 225.117 Documentation of informed consent.
- 225.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 225.119 Research undertaken without the intention of involving human subjects.
- 225.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 225.121 [Reserved]
- 225.122 Use of Federal funds.
- 225.123 Early termination of research support: Evaluation of applications and proposals.
- 225.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: December 13, 1990.

Richard E. Bissell,
Assistant Administrator for Science and
Technology.

**DEPARTMENT OF HOUSING AND
URBAN DEVELOPMENT**

24 CFR Part 60

RIN 2501-AA15

List of Subjects in 24 CFR Part 60

Human subjects, Research, Reporting and record-keeping requirements. Title 24 of the Code of Federal Regulations is amended by adding part 60 as set forth at the end of this document.¹

**PART 60 PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 60.101 To what does this policy apply?
- 60.102 Definitions.
- 60.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 60.104 [Reserved]
- 60.105 [Reserved]
- 60.106 [Reserved]
- 60.107 IRB Membership.
- 60.108 IRB functions and operations.
- 60.109 IRB review of research.
- 60.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 60.111 Criteria for IRB approval of research.
- 60.112 Review by institution.
- 60.113 Suspension or termination of IRB approval of research.
- 60.114 Cooperative research.
- 60.115 IRB records.
- 60.116 General requirements for informed consent.
- 60.117 Documentation of informed consent.
- 60.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 60.119 Research undertaken without the intention of involving human subjects.
- 60.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 60.121 [Reserved]
- 60.122 Use of Federal funds.
- 60.123 Early termination of research support: Evaluation of applications and proposals.
- 60.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: January 16, 1991.

Jack Kemp,
Secretary, U.S. Department of Housing and
Urban Development.

DEPARTMENT OF JUSTICE

28 CFR Part 46

RIN 1105-AA13

List of Subjects in 28 CFR Part 46

Human subjects, Research, Reporting and record-keeping requirements.

Title 28 of the Code of Federal Regulations is amended by adding part 46 as set forth at the end of this document.¹

**PART 46—PROTECTION OF HUMAN
SUBJECTS**

Sec.

- 46.101 To what does this policy apply?
- 46.102 Definitions.
- 46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 46.104 [Reserved]
- 46.105 [Reserved]
- 46.106 [Reserved]
- 46.107 IRB Membership.
- 46.108 IRB functions and operations.
- 46.109 IRB review of research.
- 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 46.111 Criteria for IRB approval of research.
- 46.112 Review by institution.
- 46.113 Suspension or termination of IRB approval of research.
- 46.114 Cooperative research.
- 46.115 IRB records.
- 46.116 General requirements for informed consent.
- 46.117 Documentation of informed consent.
- 46.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 46.119 Research undertaken without the intention of involving human subjects.
- 46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 46.121 [Reserved]
- 46.122 Use of Federal funds.
- 46.123 Early termination of research support: Evaluation of applications and proposals.
- 46.124 Conditions.

Authority: 5 U.S.C. 301; 28 U.S.C. 509-510; 42 U.S.C. 300v-1(b).

¹See Footnote 1 on page 28023.

Dated: December 24, 1990.

Dick Thornburgh,
Attorney General.

DEPARTMENT OF DEFENSE

32 CFR Part 219

RIN 0790-AC80

List of Subjects in 32 CFR Part 219

Human subjects, Research, Reporting and record-keeping requirements.

Title 32 of the Code of Federal Regulations is amended by revising part 219 as set forth at the end of this document.¹

PART 219—PROTECTION OF HUMAN SUBJECTS

Sec.

- 219.101 To what does this policy apply?
- 219.102 Definitions.
- 219.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 219.104 [Reserved]
- 219.105 [Reserved]
- 219.106 [Reserved]
- 219.107 IRB Membership.
- 219.108 IRB functions and operations.
- 219.109 IRB review of research.
- 219.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 219.111 Criteria for IRB approval of research
- 219.112 Review by institution.
- 219.113 Suspension or termination of IRB approval of research.
- 219.114 Cooperative research.
- 219.115 IRB records.
- 219.116 General requirements for informed consent.
- 219.117 Documentation of informed consent.
- 219.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 219.119 Research undertaken without the intention of involving human subjects.
- 219.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 219.121 [Reserved]
- 219.122 Use of Federal funds.
- 219.123 Early termination of research support: Evaluation of applications and proposals.
- 219.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: January 9, 1991.

Linda M. Bynum,
Alternate OSD Federal Register Liaison
Officer, Department of Defense.

DEPARTMENT OF EDUCATION

34 CFR Part 97

RIN 1875-AA07

List of Subjects in 34 CFR Part 97

Human subjects, Research, Reporting and record-keeping requirements.

Title 34 of the Code of Federal Regulations is amended by adding part 97 as set forth at the end of this document.¹

PART 97—PROTECTION OF HUMAN SUBJECTS

Sec.

- 97.101 To what does this policy apply?
- 97.102 Definitions.
- 97.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 97.104 [Reserved]
- 97.105 [Reserved]
- 97.106 [Reserved]
- 97.107 IRB Membership.
- 97.108 IRB functions and operations.
- 97.109 IRB review of research.
- 97.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 97.111 Criteria for IRB approval of research.
- 97.112 Review by institution.
- 97.113 Suspension or termination of IRB approval of research.
- 97.114 Cooperative research.
- 97.115 IRB records.
- 97.116 General requirements for informed consent.
- 97.117 Documentation of informed consent.
- 97.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 97.119 Research undertaken without the intention of involving human subjects.
- 97.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 97.121 [Reserved]
- 97.122 Use of Federal funds.
- 97.123 Early termination of research support: Evaluation of applications and proposals.
- 97.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: June 6, 1991.

Lamar Alexander,
U.S. Secretary of Education.

DEPARTMENT OF VETERANS AFFAIRS

38 CFR Part 16

RIN 2900-AE29

List of Subjects in 38 CFR Part 16

Human subjects, Research, Reporting and record-keeping requirements.

Title 38 of the Code of Federal Regulations is amended by adding part 16 as set forth at the end of this document.¹

PART 16—PROTECTION OF HUMAN SUBJECTS

Sec.

- 16.101 To what does this policy apply?
- 16.102 Definitions.
- 16.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 16.104 [Reserved]
- 16.105 [Reserved]
- 16.106 [Reserved]
- 16.107 IRB Membership.
- 16.108 IRB functions and operations.
- 16.109 IRB review of research.
- 16.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 16.111 Criteria for IRB approval of research.
- 16.112 Review by institution.
- 16.113 Suspension or termination of IRB approval of research.
- 16.114 Cooperative research.
- 16.115 IRB records.
- 16.116 General requirements for informed consent.
- 16.117 Documentation of informed consent.
- 16.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 16.119 Research undertaken without the intention of involving human subjects.
- 16.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 16.121 [Reserved]
- 16.122 Use of Federal funds.
- 16.123 Early termination of research support: Evaluation of applications and proposals.
- 16.124 Conditions.

¹ See Footnote 1 on page 28023.

Authority: 5 U.S.C. 301; 38 U.S.C. 210(c)(1), 4131, 4134; 42 U.S.C. 300v-1(b).
Dated: February 19, 1991.

Edward J. Derwinski
Secretary of Veterans Affairs.

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 26

RIN 2080-AA04

List of Subjects in 40 CFR Part 26

Human subjects, Research, Reporting and record-keeping requirements.

Title 40 of the Code of Federal Regulations is amended by adding part 26 as set forth at the end of this document.¹

PART 26—PROTECTION OF HUMAN SUBJECTS

- Sec.
- 26.101 To what does this policy apply?
- 26.102 Definitions.
- 26.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 26.104 [Reserved]
- 26.105 [Reserved]
- 26.106 [Reserved]
- 26.107 IRB Membership.
- 26.108 IRB functions and operations.
- 26.109 IRB review of research.
- 26.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 26.111 Criteria for IRB approval of research.
- 26.112 Review by institution.
- 26.113 Suspension or termination of IRB approval of research.
- 26.114 Cooperative research.
- 26.115 IRB records.
- 26.116 General requirements for informed consent.
- 26.117 Documentation of informed consent.
- 26.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 26.119 Research undertaken without the intention of involving human subjects.
- 26.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 26.121 [Reserved]
- 26.122 Use of Federal funds.
- 26.123 Early termination of research support: Evaluation of applications and proposals.
- 26.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

¹See Footnote 1 on page 28023.

Dated: January 28, 1991.
William K. Reilly,
Administrator.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

RIN 0991-AA71

List of Subjects in 45 CFR Part 46

Human subjects, Research, Reporting and record-keeping requirements.

Title 45 of the Code of Federal Regulations part 46 is amended, as follows:

1. An authority citation for subpart A is added to read as follows:

Authority: 5 U.S.C. 301; 42 U.S.C. 289, 42 U.S.C. 300v-1(b).

2. Subpart A is revised to read as set forth at the end of this document.¹

PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

- Sec.
- 46.101 To what does this policy apply?
- 46.102 Definitions.
- 46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 46.104 [Reserved]
- 46.105 [Reserved]
- 46.106 [Reserved]
- 46.107 IRB Membership.
- 46.108 IRB functions and operations.
- 46.109 IRB review of research.
- 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 46.111 Criteria for IRB approval of research.
- 46.112 Review by institution.
- 46.113 Suspension or termination of IRB approval of research.
- 46.114 Cooperative research.
- 46.115 IRB records.
- 46.116 General requirements for informed consent.
- 46.117 Documentation of informed consent.
- 46.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 46.119 Research undertaken without the intention of involving human subjects.
- 46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 46.121 [Reserved]
- 46.122 Use of Federal funds.
- 46.123 Early termination of research

support: Evaluation of applications and proposals.

46.124 Conditions.

Dated: March 29, 1991.

Louis W. Sullivan,
Secretary of Health and Human Services.

NATIONAL SCIENCE FOUNDATION

45 CFR Part 690

RIN 3145-AA18

List of Subjects in 45 CFR Part 690

Human subjects, Research, Reporting and record-keeping requirements.

Title 45 of the Code of Federal Regulations is amended by adding part 690 as set forth at the end of this document.¹

PART 690—PROTECTION OF HUMAN SUBJECTS

- Sec.
- 690.101 To what does this policy apply?
- 690.102 Definitions.
- 690.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 690.104 [Reserved]
- 690.105 [Reserved]
- 690.106 [Reserved]
- 690.107 IRB Membership.
- 690.108 IRB functions and operations.
- 690.109 IRB review of research.
- 690.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 690.111 Criteria for IRB approval of research.
- 690.112 Review by institution.
- 690.113 Suspension or termination of IRB approval of research.
- 690.114 Cooperative research.
- 690.115 IRB records.
- 690.116 General requirements for informed consent.
- 690.117 Documentation of informed consent.
- 690.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 690.119 Research undertaken without the intention of involving human subjects.
- 690.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 690.121 [Reserved]
- 690.122 Use of Federal funds.
- 690.123 Early termination of research support: Evaluation of applications and proposals.
- 690.124 Conditions.

Dated: December 17, 1990.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Frederick M. Bernthal,
Acting Director.

DEPARTMENT OF TRANSPORTATION

49 CFR Part 11

RIN 2105-AB74

List of Subjects in 49 CFR Part 11

Human subjects, Research, Reporting and record-keeping requirements.

Title 49 of the Code of Federal Regulations is amended by adding part 11 as set forth at the end of this document.¹

¹Due to an error in the order of the document pages submitted to the Office of the Federal Register, the text of the common rule appears at the end of the common preamble for this document at page 28012.

PART 11—PROTECTION OF HUMAN SUBJECTS

Sec.

- 11.101 To what does this policy apply?
- 11.102 Definitions.
- 11.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 11.104 [Reserved]
- 11.105 [Reserved]
- 11.106 [Reserved]
- 11.107 IRB Membership.
- 11.108 IRB functions and operations.
- 11.109 IRB review of research.
- 11.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
- 11.111 Criteria for IRB approval of research.
- 11.112 Review by institution.
- 11.113 Suspension or termination of IRB approval of research.
- 11.114 Cooperative research.
- 11.115 IRB records.

Sec.

- 11.116 General requirements for informed consent.
- 11.117 Documentation of informed consent.
- 11.118 Applications and proposals lacking definite plans for involvement of human subjects.
- 11.119 Research undertaken without the intention of involving human subjects.
- 11.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.
- 11.121 [Reserved]
- 11.122 Use of Federal funds.
- 11.123 Early termination of research support: Evaluation of applications and proposals.
- 11.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b).

Dated: February 4, 1991.

Samuel K. Skinner,

Secretary of Transportation.

[FR Doc. 91-14258 Filed 6-17-91; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Agency Forms Submitted to the Office of Management and Budget for Clearance

The following request has been submitted to the Office of Management and Budget (OMB) for clearance in compliance with the Paperwork Reduction Act (44 U.S.C. chapter 35). Expedited review by OMB has been requested as described below.

(Call PHS Reports Clearance Officer on 202-245-2100 for copies of submission)

Federal Policy for the Protection of Human Subjects—New—This submission is for approval of the information requirements associated with the common rule for the protection of human subjects of research conducted, supported or regulated by the following Federal departments and agencies: Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Department of Veterans' Affairs, Environmental Protection Agency, Department of Transportation, Central Intelligence Agency, and Department of Health and Human Services.

Adoption of the common Federal policy by these departments and agencies will implement a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. The Office of Science and Technology Policy

established an Interagency Human Subjects Coordinating Committee under the Federal Coordinating Council for Science Engineering and Technology. This group prepared a proposed Model Federal Policy for the Protection of Human Subjects that was published as a proposed policy in 1986 and again as a proposed common rule on November 10, 1988. After revision of the proposed common rule in response to public comments, the final common rule is being published elsewhere in this issue of the **Federal Register**. The common rule is based on Department of Health and Human Services (DHHS) regulations (45 CFR part 46, subpart A), the basic HHS Policy for the Protection of Human Subjects.

Respondents: Individuals or households, State or local governments, businesses or other for-profit, Federal agencies or employees, non-profit institutions, small businesses or organizations.

The total number of respondents affected by these information requirements is estimated at 3,831. The total annual response burden for these requirements including all Federal departments and agencies subject to the common rule, is estimated at 187,408 hours divided as follows: 22,982 hours for recordkeeping requirements and 164,426 hours for reporting and disclosure requirements.

Additional Information:

DHHS has submitted this request for approval to OMB on behalf of all Departments and Agencies governed by this final rule. It is critical to receive OMB review and approval for the information requirements so that the common rule for the Protection of Human Subjects may be effective 60 days after publication. Federal Departments and Agencies have ongoing research programs to which the

common rule will apply, and they are seeking the most expeditious time frame in which to begin protection of human subject policies and procedures. In addition, institutions supported or regulated by the involved Departments and Agencies have requested implementation of the final rule as soon as possible to lessen burden of compliance with numerous, sometimes inconsistent, procedures for the protection of human subjects required by the various Federal Departments and Agencies.

OMB has been requested to review and approve the information requirements in the common rule on an expedited basis no later than August 2, 1991. In keeping with the requirements for expedited review, we are publishing this announcement in the same issue as the proposed final rule. The information requirements are separately identified in the preamble to the rule, printed elsewhere in this issue. There are no separate forms or instructions for which approval is being sought.

OMB Desk Officer: Shannah Koss-McCallum.

Because of the time frame in which OMB has been asked to act on this request, any comments and recommendations for the proposed information collection should be provided directly to the OMB Desk Officer designated above by telephone at (202) 395-7316 or by express mail at the following address: Human Resources and Housing Branch, New Executive Office Building, room 3002, Washington, DC 20503.

Dated: May 31, 1991.

Sandra K. Mahkorn,

Deputy Assistant Secretary for Public Health Policy.

[FR Doc. 91-14259 Filed 6-17-91; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Parts 50 and 56**

[Docket No. 87N-0032]

RIN 0905-AC52

Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards for Clinical Investigations**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on institutional review boards (IRB's) and on informed consent to conform them to the "Federal Policy for the Protection of Human Research Subjects" (Federal Policy) published elsewhere in this issue of the **Federal Register**. Existing FDA regulations governing the protection of human subjects share a common core with the Federal Policy and implement the fundamental principles embodied in that policy.

EFFECTIVE DATE: August 19, 1991.

FOR FURTHER INFORMATION CONTACT: Richard M. Klein, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION:**I. Background**

FDA is charged by statute with ensuring the protection of the rights, safety, and welfare of human subjects who participate in clinical investigations involving articles subject to section 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), or 360j(g)), as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

In the **Federal Register** of January 27, 1981, FDA adopted regulations governing informed consent of human subjects (21 CFR part 50; 46 FR 8942) and regulations establishing standards for the composition, operation, and responsibilities of IRB's that review clinical investigations involving human subjects (21 CFR part 56; 46 FR 8958). At the same time, the Department of Health and Human Services (HHS) adopted

regulations on the protection of human research subjects (45 CFR part 46; 46 FR 8366). The FDA and HHS regulations share a common framework.

In December 1981, the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioral Research (the commission) issued its "First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research, Protecting Human Subjects." The commission recommended that all Federal departments and agencies adopt the HHS regulations (45 CFR part 46).

In May 1982, the President's Science Advisor, Office of Science and Technology Policy (OSTP), appointed an ad hoc Committee for the Protection of Human Research Subjects (the committee), under the auspices of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), to respond to the recommendations of the commission. The committee, composed of representatives and ex officio members from departments and agencies that conduct, support, or regulate research involving human subjects, developed responses to the commission in consultation with OSTP and the Office of Management and Budget (OMB).

The committee agreed that uniformity of Federal regulations on human subject protection is desirable to eliminate unnecessary regulations and to promote increased understanding by institutions that conduct federally-supported or regulated research. The committee developed a model policy which OSTP later modified and, with the concurrence of all affected Federal departments and agencies, published as a proposal in the **Federal Register** of June 3, 1986 (51 FR 20204). More than 200 comments were submitted in response to the proposal. Published elsewhere in this issue of the **Federal Register** is the final rule on the Federal Policy.

FDA concurs in that final rule. In the **Federal Register** of November 10, 1988 (53 FR 45678), the agency proposed to amend its regulations in 21 CFR parts 50 and 56 to conform them to the Federal Policy to the extent permitted by the act. The agency is committed to being as consistent with the final Federal Policy as it can be, given the unique requirements of the act and the fact that FDA is a regulatory agency that rarely supports or conducts research under its regulations. However, as explained in the proposed rule, FDA must diverge from §§ _____101(h) and _____116(d) of the Federal Policy.

FDA received 22 comments on the proposed rule from sponsors of regulated research, institutional review board members and staff, academic institutions, medical societies, and lawyers. Several comments were prepared by organizations, each representing a consortia of institutions that had been polled concerning the proposed rule.

A. General Comments

1. The majority of comments supported the agency's efforts to conform to the Federal Policy.

2. The majority of comments received concerned the proposal to amend § 56.108(b) to require that IRB's follow written guidelines for ensuring the reporting of scientific misconduct and of unanticipated problems to the IRB, institutional officials, and FDA. Two comments noted that this provision would make the IRB the institutional body that investigates alleged fraud, severely damaging the IRB/investigator relationship and possibly diminishing the effectiveness of the IRB in protecting human subjects. Several comments noted that the proposed additional reporting requirements would duplicate investigator and sponsor reporting requirements and would be difficult for the IRB to enforce. One comment said that this section may adversely affect the IRB/institution relationship and asked how FDA intended to ensure that reporting occurred. One comment interpreted the provision as applicable to animal studies and wondered whether IRB's would be responsible for contacting sponsors. One comment expressed concern that the workload of the IRB would increase and adversely affect the recruitment of new members. One comment sought to exclude Adverse Drug Reaction reports. One comment argued that the reporting requirement was unauthorized by law.

Two comments from sponsors requested that sponsor notification be added under proposed § 56.108(b), noting that an investigator engaged in misconduct is unlikely to report that misconduct to the IRB, and that the sponsor is the entity that frequently detects misconduct through its extensive monitoring practices. In addition, these comments requested clarification of the office in FDA to which scientific misconduct should be reported. Several comments requested that FDA define or clarify "scientific misconduct" and "unanticipated problems."

Since the proposed model policy was published, the Public Health Service published a final rule concerning fraud and misconduct in science (54 FR 32446,

August 8, 1989). Because that rule directs institutions to establish provisions for the investigation of alleged scientific fraud and misconduct, the mention of "scientific misconduct" has been deleted, as unnecessary, from the model policy. Because FDA only proposed to require that IRB's report scientific misconduct to be consistent with the model policy, it has deleted this requirement from its final rule. This action should allay many of the concerns expressed in the comments.

Moreover, FDA believes that the comments misconstrued the intent of § 56.108(b). This section requires simply that an IRB have procedures by which it checks to ensure in reviewing each study presented, that provision has been made in the study to notify the IRB, appropriate institutional officials, and FDA in the specified circumstances. Section 56.108(b) does not require that the IRB itself provide the notification to either the institution or to FDA, unless such reporting would not otherwise occur. Although FDA's regulations include reporting requirements for certain types of investigational articles (see, e.g., 21 CFR parts 312 (investigational drugs) and 812 (investigational devices)), there are no such provisions for other articles that may be the subject of an investigation (e.g. food additives). Because all regulated research to be conducted at an institution will come before the IRB, FDA finds that the IRB is the appropriate entity to charge with the responsibility for ensuring that reporting of the specified problems to the IRB, the institution, and the agency will occur.

3. One comment urged FDA to move toward the adoption of an assurance system as established for the other agencies within HHS to guarantee compliance with regulations for the protection of human subjects.

FDA continues to believe that it would be inappropriate for it to adopt this mechanism. As stated in the final rule in the **Federal Register** of January 27, 1981 (46 FR 8959, comment 2), the benefits of assurance from IRB's that are subject to FDA jurisdiction, but not otherwise to HHS jurisdiction, do not justify the increased administrative burdens that would result from an assurance system. FDA relies on its Bioresearch Monitoring Program, along with its educational efforts, to assure compliance with these regulations.

4. One comment expressed concern over FDA's proposed divergences from sections 101(h) and 116(d) of the Federal Policy. The comment contended that it is sometimes impossible to obtain informed consent, as defined by FDA's regulations, in foreign clinical trials.

As stated in the proposed rule (53 FR 45679), FDA does not have the authority to accept the procedures followed in a foreign country in lieu of informed consent as required by the act for studies that are conducted under a research permit that it grants. The comment did not provide any information that would compel a different conclusion.

B. Comments on Definitions

5. One comment suggested that the word "discomfort" used in proposed §§ 50.3(i) and 56.102(i) is difficult to define and is subjective.

FDA believes that the meaning of "discomfort" is sufficiently clear. FDA interprets this term to have its ordinary meaning; that is, to mean the extent to which a subject may be made uncomfortable by the article that is the subject of the research.

6. One comment asserted that proposed § 56.102(m), the definition of "IRB approval," suggests an intent to change the procedural requirements of IRB approval.

FDA proposed to add this definition to make the regulations conform to the Federal Policy and to clarify the meaning of the phrase "IRB approval" under this rule. The addition of this definition is not intended to effect a substantive change in part 56. In the preamble to its August 8, 1978 proposal of the IRB regulation (43 FR 35186 at 35197), FDA presented a thorough discussion of its authority to require IRB review.

7. One comment stated that the reference to "other institutional and Federal requirements" in proposed § 56.102(m) goes beyond FDA's ability to determine other institutional requirements and may be counterproductive where there is conflict between the institutional requirements and FDA or HHS requirements. The suggestion is made to delete "and other institutional * * * requirements."

This definition is intended to make clear that IRB approval is to be based on a determination that the proposed research is acceptable under any applicable institutional requirements, applicable law, and standards of professional conduct and practice. If there are conflicts between the institutional requirements and Federal law, those conflicts obviously must be resolved in favor of the Federal law. However, institutional requirements often address matters not addressed by Federal law. Therefore, FDA finds it appropriate to mention both institutional and Federal requirements in this definition.

8. One comment suggested substituting "clinical investigation" for the word "research" in § 56.102(m).

FDA rejects the suggestion. FDA has defined "clinical investigation" in § 56.102(c) to be synonymous with "research" (46 FR 8976). Because FDA desires to conform to the Federal Policy and in the absence of a compelling argument to diverge from it, FDA is using the word used in the Federal Policy.

9. Several comments suggested deleting "at an institution" from § 56.102(m), contending that this phrase may confuse the original intent of the meaning of IRB approval. Another comment noted that much research today is conducted outside the institutional setting.

FDA rejects the comments. In 1981, when FDA adopted the IRB regulations, FDA intentionally defined "institution" broadly to include "any public or private entity or agency" (§ 56.102(f); 46 FR 8963, comment 27). Thus, § 56.102(m) is consistent with the original intent of the IRB regulations.

10. One comment suggested revising § 56.102(m) to read "IRB approval means * * * that the research has been reviewed for undue risk to the subject and may be conducted * * *."

FDA rejects the suggestion. The suggested change does not adequately describe the role of the IRB. The IRB's review of studies and informed consent documents includes numerous considerations in addition to whether the study presents undue risks to the human subjects involved.

C. Comments on Exemptions From IRB Requirements

11. One comment requested that no exemptions from IRB requirements be granted for those populations already identified as vulnerable.

FDA did not propose that studies involving vulnerable populations be exempt from IRB review. The only exemptions from the IRB review requirements were established in the 1981 final rule (46 FR 8942; 21 CFR 56.104). The use of an investigational article is exempt from IRB review if the investigation started before July 27, 1981, before the requirement of IRB review was in effect, or if it involves an emergency use of the test article, in which case there is not time for IRB review before the article is used. The agency found that in these circumstances, the considerations that support granting an exemption outweigh those that would support denying it (46 FR 8965, comment 48). The comment did not provide any basis for reconsidering

or revising this judgment. The agency points out that the latter consideration (emergency use), which is the only basis on which a new study would be exempt, applies only to particular uses of an article and would not provide the basis for an exemption for the use of an article in a particular population. Therefore, FDA finds that this comment provides no basis for modifying its regulations.

12. One comment suggested that FDA completely exempt "minimal risk" studies from IRB review.

FDA rejects the comment. The determination of minimal risk can be made only by members of the IRB, not the investigator or the sponsor. The burden of an expedited review of a protocol to determine if it presents minimal risk is not so great as to justify the requested exemption.

D. Comments on IRB Membership

13. Three comments suggested that FDA define in § 56.107 the specific members to be included on an IRB. Several comments suggested that FDA define, in new § 56.107(c), "non-scientific" and "scientific." Two comments suggested that the IRB include "one member who has an understanding of the medical risks involved." Another comment suggested that § 56.107(c) be clarified to include a statement requiring that at least one member of the IRB have an understanding of the scientific method.

FDA rejects these comments. FDA has chosen not to prescribe professional membership requirements for IRB members. The regulations allow for flexibility in the makeup of the IRB (see 46 FR 8966, comment 55). They require, however, that there be at least one member whose concerns are in nonscience areas and one member who has the professional competency to review the proposed research, such as a physician. FDA interprets "competency" in this context to include the ability to understand the scientific method. The agency believes that the membership requirements that it has adopted are adequate to ensure that an IRB will be able to fully consider the issues presented by a study.

14. One comment suggested that the proposed change in § 56.107(a), allowing IRB's that regularly review studies that involve vulnerable categories of subjects to consider including as a member an individual knowledgeable about, and experienced in, working with vulnerable populations, will afford less human subject protection than the current regulation.

The current regulation states that an IRB that regularly reviews research involving vulnerable populations should

include as members individuals who are primarily concerned with the welfare of vulnerable subjects. Revised § 56.107(a) lists categories of subjects who are considered vulnerable and requires that the institution, or other authority, consider including individuals knowledgeable and experienced in working with these types of subjects as voting members on the IRB. This revision is not intended to lessen in any way the protections for vulnerable populations under FDA's regulations. As explained in the proposal (53 FR 45679), FDA is making this change only to conform to the language of the Federal Policy.

FDA on its own initiative is adding parenthesis to the word "reviewers" in § 56.110(b)(1) to permit a continuance of existing IRB review procedures.

E. Comments on IRB Functions and Operations

15. Several comments sought clarification of new § 56.108(b)(1) with regard to the definition and interpretation of "any unanticipated problems involving risks to human subjects and others" and the level of risk to be reported.

FDA interprets this phrase to mean an unexpected adverse experience that is not listed in the labeling for the test article. Such experience includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling but that differs from the event because of greater specificity or severity. The word "others" has previously been defined as persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials (see 53 FR 45661, 45665; November 10, 1988).

F. Comments on Expedited Review Procedures

16. One comment read the parenthetical change in § 56.110(b), "of one year or less," as affecting a change from the current regulations.

FDA disagrees with the comment. Under current regulations, the IRB may approve a study that will continue beyond 1 year, such as a longitudinal followup study. The IRB is obligated, however, under § 56.109(e) (21 CFR 56.109(e)), to conduct continuing review of the research at intervals appropriate to the degree of risk that it presents but not less than once a year.

17. One comment stated that expedited review procedures should never be used in research that involves vulnerable populations.

FDA disagrees with the comment. Expedited review procedures may only be used to review research that involves minimal risk as defined in § 56.102(i) or to review minor changes in previously approved research (§ 56.110(b)). The determination that such conditions apply must be made by the chairperson of the IRB, or by one or more experienced members of the IRB designated by the chairperson. Thus, research involving vulnerable populations will not be subject to expedited review unless a member of the IRB has affirmatively determined that the subjects will not be exposed to any greater risk of harm than they encounter in daily life or during routine physical or psychological examinations or tests, or that a change in research that has been reviewed by the whole IRB is minor. Obviously, in making these determinations, the IRB member must consider the nature of the subject population. Moreover, if expedited review is undertaken, the reviewer may exercise all the authority of the IRB, including the authority under § 56.111(a)(3) to ensure that any special problems of vulnerable populations have been addressed. Thus, FDA believes that vulnerable populations will not be involved in research that has been subject to expedited review procedures without full consideration of whether such research should be subject to expedited review at all and, if so, of their interests. Therefore, FDA does not agree with the comment.

G. Comments on Criteria for IRB Approval of Research

18. One comment suggested deleting "* * * economically or educationally disadvantaged persons * * *" from new § 56.111(a)(3), stating that it would be impossible for the IRB or the clinical investigator to make that determination.

FDA disagrees with the comment. As stated in § 56.111(b), FDA expects the IRB to make sure that adequate protections are included in those clinical investigations in which vulnerable subjects will be participating. There is no requirement for the IRB to make a determination that individual subjects are disadvantaged. However, the IRB is required to determine whether it is likely that vulnerable individuals will be involved in the study, and, if so, whether adequate safeguards have been included to protect the study subjects or whether additional safeguards are necessary.

II. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or

cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Economic and Regulatory Assessments

FDA has examined the economic consequences of the final amendments to its regulations pertaining to IRB's and to informed consent in accordance with the criteria in section 1(b) of Executive Order 12291 and found that these amendments would not be a major rule under the Executive Order. The agency also has considered the effect that the final rule would have on small entities including small businesses in accordance with the Regulatory Flexibility Act (Pub. L. 96-354). The agency certifies that there will not be a significant economic impact on a substantial number of small entities. FDA explained the basis for these conclusions in the proposal (53 FR 45681). The agency did not receive any comments that suggest contrary conclusions. This final rule contains information collections subject to the Paperwork Reduction Act of 1980. These information collections have been approved under OMB control number 0910-0130.

List of Subjects in

21 CFR Part 50

Prisoners, Reporting and recordkeeping requirements, Research, Safety.

21 CFR Part 56

Reporting and Recordkeeping requirements, Research, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, 21 CFR parts 50 and 56 are amended as follows:

PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

2. Section 50.3 is amended by revising paragraph (l) to read as follows:

§ 50.3 Definitions.

* * * * *

(l) *Minimal risk* means that the probability and magnitude of harm or

discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

* * * * *

PART 56—INSTITUTIONAL REVIEW BOARDS

3. The authority citation for 21 CFR part 56 continues to read as follows:

Authority: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701, 706, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371, 376, 381); secs. 215, 301, 351, 354-360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b-263n).

4. Section 56.102 is amended by revising paragraph (i) and by adding new paragraph (m) to read as follows:

§ 56.102 Definitions.

* * * * *

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

* * * * *

(m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

5. Section 56.104 is amended by adding new paragraph (d) to read as follows:

§ 56.104 Exemptions from IRB requirement.

* * * * *

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

6. Section 56.107 is amended by revising paragraphs (a), (b), and (c) to read as follows:

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to

promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

* * * * *

7. Section 56.108 is amended by revising paragraph (a), by removing paragraph (c), by redesignating paragraph (b) as paragraph (c), by adding a new paragraph (b), and by adding a parenthetical statement to the end of the section to read as follows:

§ 56.108 IRB functions and operations.

* * * * *

(a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in

research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

* * * * *

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130)

8. Section 56.110 is amended by revising paragraph (b) to read as follows:

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

* * * * *

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in § 56.108(c).

9. Section 56.111 is amended by revising paragraphs (a)(3) and (b) to read as follows:

§ 56.111 Criteria for IRB approval of research.

(a) * * *

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special

problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

* * * * *

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

10. Section 56.115 is amended by revising paragraph (a)(6) and by adding a parenthetical statement to the end of the section to read as follows:

§ 56.115 IRB records.

(a) * * *

(6) Written procedures for the IRB as required by § 56.108 (a) and (b).

* * * * *

(Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130)

Dated: March 29, 1991.

David A. Kessler,
Commissioner of Food and Drugs.

Louis W. Sullivan,
Secretary of Health and Human Services.
[FR Doc. 91-14260 Filed 6-17-91; 8:45 am]

BILLING CODE 4160-01-M

DEPARTMENT OF EDUCATION

34 CFR Parts 350 and 356

Protection Of Human Subjects— Disability and Rehabilitation Research: General Provisions, Disability and Rehabilitation Research: Research Fellowships

AGENCY: Department of Education.

ACTION: Interim final regulations with an opportunity to comment.

SUMMARY: The Secretary amends program regulations for the National Institute on Disability and Rehabilitation Research to add certain protections for handicapped children and mentally disabled persons who are the subjects of research conducted or sponsored by those programs. Specifically, the program regulations would require that when an institutional review board (IRB) reviews research involving these research subjects, the IRB must include at least one person who is primarily concerned with the welfare of the research subjects. The

regulations are necessary as the result of the Department of Education's (Department) withdrawal of a departure from the common regulations for the protection of human research subjects.

DATES: Comments must be received on or before August 2, 1991. These regulations take effect either August 19, 1991, or later if the Congress takes certain adjournments. If you want to know the effective date of these regulations, call or write the Department of Education contact person. A document announcing the effective date will be published in the **Federal Register**.

ADDRESSES: All comments concerning these interim final regulations should be addressed to Mr. Edward Glassman; Office of Planning, Budget and Evaluation; U.S. Department of Education, Federal Building #6, room 3127, 400 Maryland Avenue SW., Washington, DC 20202-4132.

FOR FURTHER INFORMATION CONTACT: Edward B. Glassman, Telephone: (202) 401-3132. Deaf and hearing impaired individuals may call the Federal Dual Party Relay Service at 1-800-877-8339 (In the Washington DC area, 202 708-9300) between 8 a.m. and 7 p.m. Eastern Time.

SUPPLEMENTARY INFORMATION: The Office of Science and Technology Policy, Executive Office of the President (OSTP), published a "Proposed Model Policy for the Protection of Human Subjects" in the **Federal Register** on June 3, 1986 (51 FR 20204). OSTP adopted a final policy for the protection of human research subjects on November 10, 1988 (53 FR 45660). The Final Policy adopted by OSTP was included in proposed common regulations published in the **Federal Register** on November 10, 1988 (53 FR 45661) by sixteen departments and agencies in the Executive Branch of the Federal Government, including the Department of Education. The final common regulations are published in another section of this **Federal Register** part.

The notice of proposed rulemaking (NPRM) for the common regulations specifically asked for comments addressing what effect promulgation of the Model Policy would have on each of the agencies involved in the proposed rulemaking. The Secretary proposed a departure from the common regulations that would require representation on an Institutional Review Board (IRB) of at least one person primarily concerned with the welfare of the research subjects whenever the research involves handicapped children or mentally disabled persons. As discussed below,

the Secretary has decided to withdraw this across-the-board departure in favor of program-specific regulations under those programs of the Department that are likely to support covered research that involves these research subjects.

Composition of the IRB

Comment

The Department proposed a departure to § _____.107(a) of the common regulations that would have required that, for all programs of the Department, "when an IRB reviews research that deals with handicapped children or mentally disabled persons, the IRB shall include at least one person primarily concerned with the welfare of the research subjects." The remainder of the departure reiterated the common rule's provision, which required institutions to consider representation on the IRB of persons who are knowledgeable about and experienced in working with certain vulnerable subjects if the IRB regularly reviews research involving those vulnerable subjects. Twenty-one institutions focused on this proposed departure in their comments. The majority of these comments were opposed to the proposed departure.

Some commenters, while supporting the proposed general language in § _____.107, stated their belief that the departure was not necessary because the policy in § _____.107 already addresses representation of the special concerns of vulnerable subjects on the IRB. Thus, the rights of handicapped children and mentally disabled persons should be represented on any IRB that regularly reviews proposals involving those individuals and there is nothing to be gained by emphasizing these two categories of subjects. Such an emphasis was seen as a precedent with the potential for discrimination against other categories of vulnerable subjects. When special expertise is required, IRBs already have the option, and, they believed, the obligation to seek informed consultants. However, one commenter stated "If in future staffing of our IRB, someone with expertise in this area is available and willing to serve, we would be happy to encourage such participation."

One commenter suggested that only when an IRB regularly reviews research that deals with handicapped children or mentally disabled persons should the IRB include at least one person primarily concerned with the welfare of the research subjects. Otherwise, consultation should take place when appropriate. Another suggestion was that handicapped children be added to the list of examples of vulnerable

subjects for which an IRB that regularly reviews research might want to consider inclusion of one or more members who are knowledgeable about and experienced in working with these subjects.

Some commenters objected to the lack of consistency among Federal agencies and cited the Department of Education's proposed departure as inconsistent with the purpose of the common rule. One commenter indicated that the departure would not pose any problem.

Response

The language of the proposed departure was rooted in the Secretary's concern that the welfare of research subjects who are handicapped children or mentally disabled persons be adequately protected because of the diminished capacity of such persons to protect their own interests and their corresponding greater potential for harm. It should be noted that, while the common rule does, in general, protect the interests of vulnerable populations, it does not specifically command representation of their interests in all cases. For example, the common rule only requires that when an IRB regularly reviews research involving vulnerable subjects, consideration should be given to including on the IRB a researcher experienced in working with such subjects. Thus, the Department believes it is appropriate to offer special protection for handicapped children and mentally disabled persons, and the protection proposed in the departure would have satisfied that need.

The comments also appear to misunderstand the intent of the Department's proposed departure. Some commenters believed that the departure would require that an IRB include a permanent member to represent the special populations covered by the departure. Others appeared to believe that the departure would apply to all research of the institution that involved the special populations covered by the departure. The proposed departure would have produced neither of these results. Instead, the proposed departure would have required the addition of one member on an *ad hoc* basis only when the research is sponsored or funded by the Department of Education and purposefully requires the inclusion of handicapped children or mentally disabled persons.

As explained above, the Secretary believes that there is a special need to protect handicapped children and mentally disabled persons. However, given the broad policy objective of providing consistent treatment through common regulations, the Secretary has

decided that the IRB special representation requirements contained in the proposed departure are not necessary for most of the programs of the Department, because most programs of the Department do not support research likely to involve those persons. Thus, the Secretary has decided to withdraw the departure. However, the Secretary believes that the concerns addressed by the proposed departure have a particular urgency in those programs of the Department that support a significant amount of research involving handicapped children and mentally disabled persons. Therefore, the Secretary is amending the regulations for the programs of the National Institute on Disability and Rehabilitation Research (34 CFR parts 350 and 356) to ensure that the protections that would have been afforded under the departure are implemented in those specific programs.

Although the Secretary has decided to publish this regulation in final form, due to the strong public interest created by the proposed departure, and because a number of commenters appeared to misunderstand the effect of the proposed rule, the Secretary has also decided to offer the public an additional opportunity to comment on the final rule. The address to which commenters should send their comments and the date by which those comments must be received is stated at the beginning of this preamble.

Changes

In the notice of proposed rulemaking, the proposed departure was stated as follows: "When an IRB reviews research that deals with handicapped children or mentally disabled persons, the IRB must include at least one person primarily concerned with the welfare of the research subjects." The Secretary has decided to change this language in the program-specific regulations adopted in this document to make clear that the regulation specifically protects handicapped children and mentally disabled persons when those persons are purposefully included in a research protocol, rather than incidentally. Therefore, the language has been changed to state: "When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons in the research sample, the IRB must include at least one person primarily concerned with the welfare of the research subjects."

Executive Order 12291

These regulations have been reviewed in accordance with Executive Order 12291. They are not classified as major because they do not meet the criteria for major regulations established under the Order.

Regulatory Flexibility Act Certification

The Secretary certifies that these interim final regulations will not have a significant economic impact on a substantial number of small entities.

The small entities that are affected by these interim final regulations are small institutions receiving research grants or contracts under the programs of the National Institute on Disability and Rehabilitation Research. However, the regulations do not have a significant economic impact on these entities because the regulations do not impose excessive regulatory burdens. These regulations impose minimal requirements that are necessary to ensure the proper treatment of handicapped children and mentally disabled persons under the programs of the National Institute on Disability and Rehabilitation Research.

Invitation To Comment

Interested persons are invited to submit comments and recommendations regarding these interim final regulations. Comments are specifically invited on whether other research programs of the Department should have added protections for handicapped children and mentally disabled persons.

All comments submitted in response to these regulations will be available for public inspection, during and after the comment period, in room 3127, 400 Maryland Avenue, SW., Washington, DC between the hours of 9 a.m. and 4:30 p.m., Monday through Friday of each week except Federal holidays.

To assist the Department in complying with the specific requirements of Executive Order 12291 and the Paperwork Reduction Act of 1980 and their overall requirement of reducing regulatory burden, the Secretary invites comment on whether there may be further opportunities to reduce any regulatory burdens found in these interim final regulations.

Assessment of Educational Impact

The Secretary has determined that the regulations in this document do not require transmission of information that is being gathered by or is available from any other agency or authority of the United States.

List of Subjects*34 CFR Part 350*

Education, Education of the handicapped, Educational research, Grant programs—education.

34 CFR Part 356

Education, Education research, Fellowships.

Dated: June 6, 1991.

Lamar Alexander,
Secretary of Education.

(Catalog of Federal Domestic Assistance Number does not apply.)

The Secretary amends title 34 of the Code of Federal Regulations by amending parts 350 and 356 as follows:

PART 350—DISABILITY AND REHABILITATION RESEARCH: GENERAL PROVISIONS

1. The authority citation for part 350 continues to read as follows:

Authority: 29 U.S.C. 760–762, unless otherwise noted.

2. Section 350.3 is amended by revising paragraph (d) and the authority citation at the end of the section to read as follows:

§ 350.3 What regulations apply to these programs?

* * * * *

(d)(1) The regulations in 34 CFR part 97, PROTECTION OF HUMAN SUBJECTS, except § 97.107(a).

(2) Each Institutional Review Board (IRB) established under part 97 must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas. When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include

at least one person primarily concerned with the welfare of these research subjects. If an IRB regularly reviews another vulnerable category of subjects, such as non-handicapped children, prisoners, pregnant women, or handicapped adults, consideration must also be given to the inclusion of one or more individuals who are knowledgeable about the experience in working with these subjects.

(Authority: 20 U.S.C. 761a, 762, 42 U.S.C. 300v-1(b))

PART 356—DISABILITY AND REHABILITATION RESEARCH: RESEARCH FELLOWSHIPS

3. The authority citation for part 356 continues to read as follows:

Authority: 29 U.S.C. 761a(d), unless otherwise noted.

4. Section 356.3 is amended by revising paragraph (c) and the authority citation at the end of the section to read as follows:

§ 356.3 What regulations apply to this program?

* * * * *

(c)(1) The regulations in 34 CFR part 97, PROTECTION OF HUMAN SUBJECTS, except § 97.107(a).

(2) Each Institutional Review Board (IRB) established under part 97 must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas. When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these research subjects. If an IRB regularly reviews another vulnerable category of subjects, such as non-handicapped children,

prisoners, pregnant women, or handicapped adults, consideration must also be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(Authority: 29 U.S.C. 761a(d), 42 U.S.C. 300v-1(b))

[FR Doc. 91-14261 Filed 6-17-91; 8:45 am]
BILLING CODE 4000-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

45 CFR Part 46

Federal Policy for the Protection of Human Subjects: Additional Protections for Children Involved as Subjects in Research

AGENCY: Department of Health and Human Services.

ACTION: Technical amendment.

SUMMARY: This technical amendment is to correct a reference in 45 CFR part 46 subpart D (Additional Protection for Children Involved as Subjects in

Research) to subpart A of that part of the **Federal Register**.

In the revision to subpart A, published elsewhere in this issue, the numbering of exemptions in 45 CFR part 46.101(b) changes.

The reference to those exemptions in subpart D 45 CFR part 46.401(b) is now amended accordingly.

EFFECTIVE DATE: This regulation shall become effective on August 19, 1991.

FOR FURTHER INFORMATION CONTACT: Dr. Joan P. Porter, staff director, Interagency Human Subjects Coordinating Committee, building 31, room 5B59, Bethesda, Maryland 20892. Telephone (301) 496-7005.

List of Subjects in 45 CFR Part 46

Human subjects, Research, Reporting and record-keeping requirements, Infants and children.

PART 46—PROTECTION OF HUMAN SUBJECTS

1. The authority for part 46 is revised to read:

Authority: 5 U.S.C. 30; Sec. 474(a), 88 Stat. 352 [42 U.S.C. 2891-3(a)].

2. In subpart D—Additional Protections for Children Involved as Subjects in Research, § 46.401, paragraph (b) is revised to read as follows:

§ 46.401 To what do these regulations apply?

* * * * *

(b) Exemptions at § 46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at § 46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at § 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

* * * * *

Dated: March 29, 1991.

Louis W. Sullivan,
Secretary of Health and Human Services.
[FR Doc. 91-14262 Filed 6-17-91; 8:45 am]

BILLING CODE 4140-01-M

Editorial Note: This reprint incorporates a correction document published in the **Federal Register** of June 28, 1991.

Appendix C

Code of Federal Regulations, Title 45 Part 46

Subpart A. Federal Policy for the Protection of Human Subjects
(Basic DHHS Policy for Protection of Human
Research Subjects)

Subpart B. Additional DHHS Protections Pertaining to Research,
Development, and Related Activities Involving
Fetuses, Pregnant Women, and Human In Vitro
Fertilization

Subpart C. Additional DHHS Protections Pertaining to
Biomedical and Behavioral Research Involving
Prisoners as Subjects

Subpart D. Additional DHHS Protections for Children Involved as
Subjects in Research

Subpart A: Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protec- tion of Human Research Sub- jects)

Source: 56 FR 28003, June 18, 1991.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any Federal Department or Agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each Department or Agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.

(1) Research that is conducted or supported by a Federal Department or Agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a Federal Department or Agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an Institutional Review Board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. (c) Department or Agency heads retain final judgment as to whether a particular activity is covered by this policy. (d) Department or Agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Department or Agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy. (e) Compliance with this policy requires compliance with pertinent Federal laws or regulations which provide additional protections for human subjects. (f) This policy does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. (g) This policy

does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research. (h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the Department or Agency head, notices of these actions as they occur will be published in the **Federal Register** or will be otherwise published as provided in Department or Agency procedures. (i) Unless otherwise required by law, Department or Agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes or research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the Department or Agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services (DHHS), and shall also publish them in the **Federal Register** or in such other manner as provided in Department or Agency procedures.¹

§46.102 Definitions

(a) *Department or Agency head* means the head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated. (b) *Institution* means any public or private entity or Agency (including Federal, State, and other agencies). (c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. (d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research

¹ Institutions with DHHS-approved assurances on file will abide by provisions of Title 45 CFR Part 46 Subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR Part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, Subparts B and C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. (e)

Research subject to regulation, and similar terms are intended to encompass those research activities for which a Federal Department or Agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a Federal Department or Agency solely as part of the Department's or Agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor). (f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (g) *IRB* means an Institutional Review Board established in accord with and for the purposes expressed in this policy. (h) *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements. (i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (j) *Certification* means the official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall provide written assurance satisfactory to the Department or Agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual Department or Agency heads shall accept existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, National Institutes Health, DHHS, and approved for Federal wide use by that office. When the existence of a DHHS approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to Department and Agency heads shall also be made to the Office for Protection from Research Risks, National Institutes of Health, DHHS. (b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Department or Agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to Department- or Agency supported or regulated research and need not be applicable to any research exempted or waived under §46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship

between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Department or Agency head, unless in accord with §46.103(a) of this policy, the existence of a DHHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, National Institutes of Health, DHHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. (c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the Department or Agency head prescribes. (d) The Department or Agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the Department or Agency and such experts or consultants engaged for this purpose as the Department or Agency head determines to be appropriate. The Department or Agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution. (e) On the basis of this evaluation, the Department or Agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Department or Agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval. (f) Certification is required when the research is supported by a Federal Department or Agency and not otherwise exempted

or waived under §46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this policy has been reviewed and approved by the IRB.

Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the Department or Agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the Department or Agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§§46.104—46.106 [Reserved]

§46.107 IRB membership

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. (b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession. (c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. (d) Each IRB shall include at least one

member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. (e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. (f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§46.108 IRB functions and operations

In order to fulfill the requirements of this policy each IRB shall: (a) Follow written procedures in the same detail as described in §46.103(b)(4) and to the extent required by §46.103(b)(5). (b) Except when an expedited review procedure is used (see §46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting

§46.109 IRB review of research

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy. (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects. (c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117. (d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. (e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research

(a) The Secretary, HHS, has established, and published as a Notice in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the Federal Register. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, DHHS, Bethesda, Maryland 20892. (b) An IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108(b). (c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure. (d) The Department or Agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§46.111 Criteria for IRB approval of research

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public

policy) as among those research risks that fall within the purview of its responsibility. (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116. (5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117. (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§46.112 Review by institution

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Department or Agency head. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.114 Cooperative research

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the Department or Agency head, an

institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following: (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects. (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. (3) Records of continuing review activities. (4) Copies of all correspondence between the IRB and the investigators. (5) A list of IRB members in the same detail as described in §46.103(b)(3). (6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5). (7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5). (b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the Department or Agency at reasonable times and in a reasonable manner. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.116 General requirements for informed consent

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the

institution or its agents from liability for negligence. (a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject: (1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental; (2) a description of any reasonably foreseeable risks or discomforts to the subject; (3) a description of any benefits to the subject or to others which may reasonably be expected from the research; (4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject; (5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained; (6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained; (7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and (8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (b) additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject: (1) a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable; (2) anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent; (3) any additional costs to the subject that may result from participation in the research; (4) the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject; (5) a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and (6) the approximate number of subjects involved in the study. (c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that: (1) the research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those

programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and (2) the research could not practicably be carried out without the waiver or alteration. (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. (e) The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. (f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.117 Documentation of informed consent

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form. (b) Except as provided in paragraph (c) of this section, the consent form may be either of the following: (1) A written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or (2) A short form written consent document stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form. (c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: (1) That the only record linking

the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

§46.118 Applications and proposals lacking definite plans for involvement of human subjects

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101 (b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Department or Agency.

§46.119 Research undertaken without the intention of involving human subjects

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the Department or Agency, and final approval given to the proposed change by the Department or Agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency

(a) The Department or Agency head will evaluate all

applications and proposals involving human subjects submitted to the Department or Agency through such officers and employees of the Department or Agency and such experts and consultants as the Department or Agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. (b) On the basis of this evaluation, the Department or Agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds

Federal funds administered by a Department or Agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals

(a) The Department or Agency head may require that Department or Agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the Department or Agency head finds an institution has materially failed to comply with the terms of this policy. (b) In making decisions about supporting or approving applications or proposals covered by this policy the Department or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Department or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to Federal regulation).

§46.124 Conditions

With respect to any research project or any class of research projects the Department or Agency head may

impose additional conditions prior to or at the time of approval when in the judgment of the Department or Agency head additional conditions are necessary for the protection of human subjects.

Subpart B: Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975; 43 FR 1758, January 11, 1978; 43 FR 51559, November 3, 1978.

§46.201 Applicability

(a) The regulations in this subpart are applicable to all Department of Health and Human Services grants and contracts supporting research, development, and related activities involving: (1) the fetus, (2) pregnant women, and (3) human *in vitro* fertilization. (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart. (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Purpose

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§46.203 Definitions

As used in this subpart: (a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services (DHHS) to whom authority has been delegated. (b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus. (c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable. (d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The

Secretary may from time to time, taking into account medical advances, publish in the **Federal Register** guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant. (e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable. (f) "Dead fetus" means a fetus *ex utero* which exhibits neither heart beat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached). (g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

§46.204 Ethical Advisory Boards

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these Board(s) shall be so selected that the Board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No Board member may be a regular, full-time employee of the Department of Health and Human Services. (b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures. (c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint. (d) [Nullified under Public Law 103-43, June 10, 1993]

§46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties: (1) determine that all aspects of the activity meet the requirements of this subpart; (2) determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision

has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen); (3) carry out such other responsibilities as may be assigned by the Secretary. (b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in §46.120 of Subpart A of this part. (c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

§46.206 General limitations

(a) No activity to which this subpart is applicable may be undertaken unless: (1) appropriate studies on animals and nonpregnant individuals have been completed; (2) except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity; (3) individuals engaged in the activity will have no part in: (i) any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and (4) no procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity. (b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity. Source: 40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638, Nov. 6, 1975.

§46.207 Activities directed toward pregnant women as subjects

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal. (b) An activity permitted under paragraph (a) of this

section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) the purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§46.208 Activities directed toward fetuses in utero as subjects

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. (b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects

(a) Until it has been ascertained whether or not a fetus *ex utero* is viable, a fetus *ex utero* may not be involved as a subject in an activity covered by this subpart unless: (1) there will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or (2) the purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability. (b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless: (1) vital functions of the fetus will not be artificially maintained, (2) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and (3) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means. (c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part. (d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or

whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§46.210 Activities involving the dead fetus, fetal material, or the placenta

Activities involving the dead fetus, mascerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§46.211 Modification or waiver of specific requirements

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the **Federal Register**.

Subpart C: Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov. 16, 1978.

§46.301 Applicability

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects. (b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law. (c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of

this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions

As used in this subpart: (a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated. (b) "DHHS" means the Department of Health and Human Services. (c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. (d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§46.304 Composition of Institutional Review Boards where prisoners are involved

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board. (b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that: (1) the research under review represents one of the categories of research permissible under §46.306(a)(2); (2) any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the

value of such advantages in the limited choice environment of the prison is impaired; (3) the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers; (4) procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project; (5) the information is presented in language which is understandable to the subject population; (6) adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and (7) where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact. (b) The Board shall carry out such other duties as may be assigned by the Secretary. (c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if: (1) the institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and (2) in the judgment of the Secretary the proposed research involves solely the following: (A) study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects; (B) study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects; (C) research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the **Federal Register**, of his intent to approve such research; or (D) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-

being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the **Federal Register**, of the intent to approve such research. (b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D: Additional DHHS Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983; 56 FR 28032, June 18, 1991.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services. (1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint. (2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type. (b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed. (c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of Subpart A are applicable to this subpart.

§46.402 Definitions

The definitions in §46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart: (a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. (b) "Assent" means a child's affirmative agreement to participate in research. Mere

failure to object should not, absent affirmative agreement, be construed as assent. (c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research. (d) "Parent" means a child's biological or adoptive parent. (e) "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk

DHHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that: (a) the risk is justified by the anticipated benefit to the subjects; (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in

their actual or expected medical, dental, psychological, social, or educational situations; (c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

DHHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if: (a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent

requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A. (b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (c) In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk

and anticipated benefit to the research subjects, and their age, maturity, status, and condition. (d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of Subpart A. (e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards

(a) Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. (b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Appendix D

Code of Federal Regulations, Title 21 Parts 50 and 56

Part 50: Protection of Human Subjects

Subpart A. General Provisions

Subpart B. Informed Consent of Human Subjects

Part 56: Institutional Review Boards

Subpart A. General Provisions

Subpart B. Organization and Personnel

Subpart C. IRB Functions and Operations

Subpart D. Records and Reports

Subpart E. Administrative Actions for Noncompliance

Part 50: Protection of Human Subjects

Subpart A: General Provisions

Source: 45 FR 36390, May 30, 1980, unless otherwise noted.

§50.1 Scope

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 406, 409, 502, 503, 505, 510, 513–516, 518–520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354–360F of the Public Health Service Act. (b) References in this part to regulatory sections of the

Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§50.3 Definitions

As used in this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 *et seq.* as amended (21 U.S.C. 321–392)). (b) *Application for research or marketing permit* includes: (1) A color additive petition, described in part 71. (2) A food additive petition, described in parts 171 and 571. (3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §170.30 and §570.30. (4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in §180.1. (5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act. (6) An investigational new drug application, described in part 312 of this chapter. (7) A new drug application, described in part 314. (8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part

of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320. (9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330. (10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter. (11) Data and information about an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for these drugs, described in §314.300 of this chapter. (12) An application for a biologics license, described in part 601 of this chapter. (13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601. (14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809. (15) An *Application for an Investigational Device Exemption*, described in part 812. (16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513. (17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514. (18) An application for premarket approval of a medical device, described in section 515. (19) A product development protocol for a medical device, described in section 515. (20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act. (21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in §1010.4. (22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in §1010.5. (c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. (d) *Investigator* means an individual who

actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (e) *Sponsor* means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators. (f) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency. (g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (h) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The word *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part. (i) *Institutional review board (IRB)* means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act. (j) *Test article* means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n). (k) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (l) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. (m) *Family member* means any one of the following legally competent persons: spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Subpart B: Informed Consent of Human Subjects

Source: 46 FR 8951, Jan. 27, 1981, unless otherwise noted.

§50.20 General requirements for informed consent

Except as provided in §50.23 and §50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§50.23 Exception from general requirements

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article except as provided in paragraph (b) of this section, both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: (1) The human subject is confronted by a life threatening situation necessitating the use of the test article. (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject. (3) Time is not sufficient to obtain consent from the subject's legal representative. (4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. (b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. (c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article. (d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administra-

tion of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met. (i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND. (ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness. (iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug. (iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission. (v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by §56.115(a)(2) of this chapter. (vi) DOD has explained: (A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional; (B) The nature

of the disease or condition for which the preventive or therapeutic treatment is intended; and (C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug. (vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient. (viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product. (ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section. (x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter. (xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product. (xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence. (xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request. (xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use. (xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria. (xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the **Federal Register** describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information. (xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law. (2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This

IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by §56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review. (3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve: (i) The required information sheet; (ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written); (iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and (iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved. (4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed. (5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

§50.24 Exception from informed consent requirements for emergency research

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following: (1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions. (2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation. (3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) Subjects are facing a life-threatening situation that necessitates intervention; (ii) Appropriate animal and other preclinical studies have been

conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. (4) The clinical investigation could not practicably be carried out without the waiver. (5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review. (6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with §50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section. (7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review. (b) The IRB is respon-

sible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible. (c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with §56.115(b) of this chapter. (d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §312.30 or §812.35 of this chapter. (e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

§50.25 Elements of informed consent

(a) *Basic elements of informed consent.* In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. (2) A description of any reasonably foreseeable risks or discomforts to the subject. (3) A description of any benefits to the subject or to others which may reasonably be expected from the research. (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject. (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (b) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject: (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable. (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (3) Any additional costs to the subject that may result from participation in the research. (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (6) The approximate number of subjects involved in the study. (c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective. (d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical

care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

§50.27 Documentation of informed consent

(a) Except as provided in §56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form. (b) Except as provided in §56.109(c), the consent form may be either of the following: (1) A written consent document that embodies the elements of informed consent required by §50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed. (2) A *short form* written consent document stating that the elements of informed consent required by §50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

Part 56: Institutional Review Boards

Subpart A: General Provisions

§56.101 Scope

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under section 505(i) and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations. (b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§56.102 Definitions

As used in this part: (a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 *et seq.*, as amended (21 U.S.C. 321-392)). (b) *Application for research or marketing permit* includes: (1) A color additive petition, described in part 71. (2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in §170.35. (3) A food additive petition, described in part 171. (4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in §180.1. (5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act. (6) An investigational new drug application, described in part 312 of this chapter. (7) A new drug application, described in part 314. (8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320. (9) Data and information regarding an over-the counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in part 330. (10) An application for a biological product license, described in part 601. (11) An application for a biologics license, described in part 601 of this chapter. (12) An *Application for an Investigational Device Exemption*, described in parts 812 and 813. (13) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in part 860. (14) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in part 861. (15) An application for premarket approval of a medical device for human use, described in section 515 of the act. (16) A product development protocol for a medical device for human use, described in section 515 of the act. (17) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act. (18) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in §1010.4. (19) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety perfor-

mance standard, as described in §1010.5. (20) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in subpart D of part 1003. (c) *Clinical investigation* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous for purposes of this part. (d) *Emergency use* means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. (e) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. (f) *Institution* means any public or private entity or agency (including Federal, State, and other agencies). The term *facility* as used in section 520(g) of the act is deemed to be synonymous with the term *institution* for purposes of this part. (g) *Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase *institutional review committee* as used in section 520(g) of the act. (h) *Investigator* means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. (i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (j) *Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an

investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators. (k) *Sponsor-investigator* means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator. (l) *Test article* means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354–360F of the Public Health Service Act. (m) *IRB approval* means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

§56.103 Circumstances in which IRB review is required

(a) Except as provided in §56.104 and §56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part. (b) Except as provided in §56.104 and §56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration. (c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

§56.104 Exemptions from IRB requirement

The following categories of clinical investigations are exempt from the requirements of this part for IRB review: (a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981. (b) Any investigation commenced before July 27, 1981 and was not otherwise

subject to requirements for IRB review under Food and Drug Administration regulations before that date. (c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. (d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

§56.103 Circumstances in which IRB review is required

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B: Organization and Personnel

§56.107 IRB membership

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural background, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects. (b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely

of members of one profession. (c) Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas. (d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution. (e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. (f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Subpart C: IRB Functions and Operations

§56.108 IRB functions and operations

In order to fulfill the requirements of these regulations, each IRB shall: (a) Follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects. (b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval. (c) Except when an expedited review procedure is used (see §56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting. (Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130).

§56.109 IRB review of research

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations. (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §50.25. The IRB may require that information, in addition to that specifically mentioned in §50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects. (c) An IRB shall require documentation of informed consent in accordance with §50.27 of this chapter, except as follows: (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or (2) The IRB may, for some or all subjects, find that the requirements in §50.24 of this chapter for an exception from informed consent for emergency research are met. (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research. (e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under §50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under §50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination. (f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. (g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under §50.24 of this chapter a copy of information that has been publicly disclosed under §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

§56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research

(a) The Food and Drug Administration has established, and published in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the **Federal Register**. (b) An IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited review procedure set forth in §56.108(c). (c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure. (d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§56.111 Criteria for IRB approval of research

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied: (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility. (3) Selection of subjects is equitable. In making this assessment the IRB

should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons. (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50. (5) Informed consent will be appropriately documented, in accordance with and to the extent required by §50.27. (6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. (b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§56.112 Review by institution

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§56.113 Suspension or termination of IRB approval of research

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§56.114 Cooperative research

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D: Records and Reports

§56.115 IRB records

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following: (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects. (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. (3) Records of continuing review activities. (4) Copies of all correspondence between the IRB and the investigators. (5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant. (6) Written procedures for the IRB as required by §56.108 (a) and (b). (7) Statements of significant new findings provided to subjects, as required by §50.25. (b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. (c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section. (Information collection requirements in this section were approved by the Office of Management and Budget (OMB) and assigned OMB control number 0910-0130)

Subpart E: Administrative Actions for Noncompliance

§56.120 Lesser administrative actions

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to

the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations. (b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may: (1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB; (2) Direct that no new subjects be added to ongoing studies subject to this part; (3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or (4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct interest in the agency's action of the deficiencies in the operation of the IRB. (c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

§56.121 Disqualification of an IRB or an institution

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under §56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in part 16. (b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that: (1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and (2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation. (c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the

Federal Register. (d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in §56.123.

§56.122 Public disclosure of information regarding revocation

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under part 20.

§56.123 Reinstatement of an IRB or an institution

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under §56.121(c).

§56.124 Actions alternative or additional to disqualification

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

Appendix E

Protection of Human Subjects

DOE O 443.1B - Protection of Human Subjects

ORDER

DOE O 443.1B

Approved: 3-17-2011

PROTECTION OF HUMAN RESEARCH SUBJECTS



U.S. DEPARTMENT OF ENERGY
Office of Science

PROTECTION OF HUMAN RESEARCH SUBJECTS

1. **PURPOSE.** To establish Department of Energy (DOE)-specific policy and principles for the protection of human subjects involved in DOE research, and DOE procedures and responsibilities for implementing the policy and requirements set forth in Title 45 Code of Federal Regulations (CFR) Part 46, 10 CFR Part 745, and the Secretarial Policy Memorandum on Military or Intelligence-Related Human Subject Research, December 9, 2009.
2. **CANCELLATION.** This Order cancels DOE O 443.1A, *Protection of Human Subjects*, dated 12-20-07; and DOE P 443.1A, *Protection of Human Subjects*, dated 12-20-07.

Cancellation of a directive does not, by itself, modify or otherwise affect any contractual or regulatory obligation to comply with the Order. Contractor Requirements Documents (CRDs) that have been incorporated into a contract remain in effect throughout the term of the contract unless and until the contract or regulatory commitment is modified to either eliminate requirements that are no longer applicable or substitute a new set of requirements.

3. **APPLICABILITY.**

- a. **Departmental Applicability.** Except for exemption in paragraph 3.c., this Order applies to all Departmental elements.

The Administrator of the National Nuclear Security Administration (NNSA) shall ensure that NNSA employees, contractors, and elements comply with their respective responsibilities under this directive. Nothing in this Order shall be construed to interfere with the NNSA Administrator's authority under Section 3212(d) of Public Law (P.L.) 106-65 to establish Administration-specific policies, unless disapproved by the Secretary.

In accordance with the responsibilities and authorities assigned by Executive Order 12344, codified at 50 CFR Parts 2406 and 2511, and to ensure consistency throughout the joint Navy/DOE Naval Nuclear Propulsion Program, the Deputy Administrator for Naval Reactors (Director) will implement and oversee requirements and practices pertaining to this Directive for activities under the Director's cognizance, as deemed appropriate.

- b. **DOE Contractors.** Except for the exemption in paragraph 3.c., the Contractor Requirements Document (CRD), Attachment I, sets forth the requirements of this Order that shall apply to contracts that include the CRD. The CRD shall be included in contracts (i.e., those contracts that include the clause at 48 CFR Part (DEAR) 970.5204-2, Laws, regulations, and DOE directives) for the management or operation of a DOE-owned or -leased facility that involves human subjects research (HSR) as defined in paragraph 7.h., and comprehensively explained in

Paragraph 4.a., irrespective of the party conducting the HSR under the contract. For all other contracts that involve HSR, the applicable requirements set forth in the CRD shall be included in the contract terms and conditions as appropriate.

c. Exemptions for DOE O 443.1B.

Any requests for partial or full exemptions from the requirements of this Order shall be submitted in writing to the Human Subjects Protection (HSP) Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager). An exemption may be recommended to the Secretary or the Secretary's designee by the HSP Program Manager (or by the NNSA HSP Program Manager when an NNSA element is involved) after concurrence by the DOE Institutional Official (see paragraph 7f). The basis for granting or denying exemption requests shall be set forth in writing.

Exemption. Bonneville Power Administration is exempt from the requirements of DOE O 443.1B.

4. REQUIREMENTS. Research using human subjects provides important medical and scientific benefits to individuals and to society. The need for this research does not, however, outweigh the need to protect individual rights and interests. DOE policy regarding this issue is established in the Federal Policy for the Protection of Human Subjects, 45 CFR Part 46, Protection of Human Subjects, and in 10 CFR Part 745, DOE's implementation of Subpart A of 45 CFR Part 46.

a. Approvals.

- (1) No HSR conducted with DOE funding, at DOE institutions (regardless of funding source), or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research, shall be initiated without both a Federal-wide Assurance (FWA) and approval by the cognizant Institutional Review Board (IRB) in accordance with 10 CFR Part 745.103.
- (2) It is Departmental policy that Human Terrain Mapping (HTM), defined in paragraph 7.i., is managed as HSR and is subject to this Order.
 - (a) HTM projects, conducted with DOE funding, at DOE sites/institutions (regardless of funding source), or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research, shall be strictly limited to only those projects involving the analysis and modeling of de-identified data.
 - (b) Statements of work for HTM projects shall be submitted to the HSP Program Manager (and when an NNSA element is involved,

the NNSA HSP Program Manager), for DOE Headquarters review and approval prior to initiation. If the project is to be conducted by or for the intelligence community, the Office of Intelligence must also review and approve it prior to initiation. The HSP Program Manager(s) and the Office of Intelligence shall engage the recognized DOE site IRB, and as needed, the principal investigator (PI) and/or sponsor, in clarifying whether the proposed project is HTM and if so, that the data to be used will be de-identified. Additionally, the PI will be asked to provide written verification that only de-identified HTM data (as defined in paragraph 7d) will be used.

- (c) The recognized DOE site IRB is the only entity authorized to determine whether the HTM data received by the PI after project initiation meets DOE criteria for de-identification. If the DOE site does not manage or operate its IRB, then the Central DOE IRB shall be the responsible IRB.
 - (d) All Work for Others funded projects, including HTM activities, shall comply with DOE O 481.1C, *Work for Others (Non-Department of Energy Funded Work)*, dated 1-24-05.
 - (e) If, in the case the sponsor requests assistance in the de-identification of HTM data prior to start of any work on the sponsor's project and/or re-identification of data following completion of the project, DOE sites may provide such services under a separate contract and/or task order with the sponsor by following the appropriate DOE standard operating procedure approved by the DOE Institutional Official, DOE Office of Science.¹
- b. Solicitations. Any solicitation issued by a DOE element for research involving human subjects shall require compliance with the requirements of this Order, 10 CFR Part 745, and 45 CFR Part 46.
 - c. Contracts, Financial Assistance Agreements, and Other Agreements. Any DOE contract, financial assistance agreement, or other agreement involving HSR shall require compliance with the requirements set forth in the CRD associated with

¹ It should be noted that: 1) only limited communications, if needed, may take place between the organization de-identifying and/or re-identifying the sponsor's data and the organization performing work on the sponsor's task; b) the identified dataset shall not be shared with the individual who will perform work on the sponsor's task; and c) the de-identified dataset shall be sent directly by the sponsor to the individual performing work on the sponsor's task and not by the organization at the DOE site that de-identified it.

this Order (Attachment I), 10 CFR Part 745, and 45 CFR Part 46. See also CRD (Attachment 1).

- d. Notification. The Human Subjects Protection Program Manager (HSP) Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager) shall be:
- (1) Notified in writing prior to issuance of any new proposal involving HSR, even if it meets the regulatory definition of exempt HSR as outlined in 10 CFR Part 745.101(b), that involves:
 - (a) an institution without an established IRB;
 - (b) a foreign country;
 - (c) a potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);
 - (d) research subjects in a protected class (fetuses, pregnant women, and in vitro fertilization; prisoners; or children); or
 - (e) the generation or use of classified or unclassified controlled information.
 - (2) The HSP Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager) shall be notified immediately upon a finding of a suspected or confirmed data breach involving Personally Identifiable Information (PII) in printed or electronic form and reported to the DOE-Cyber Incident Response Capability in accordance with the requirements of DOE O 206.1. The appropriate HSP Program Manager shall also be informed of any corrective actions taken and shall concur on the plan for any remaining corrective actions.
 - (3) The appropriate HSP Program Manager shall be notified in writing within 48 hours, with a description of corrective actions taken, and shall concur on the plan for any remaining corrective actions, following:
 - (a) significant adverse events, unanticipated problems, and complaints about the research, suspension or termination of IRB approval of research;
 - (b) known or potential incidents of noncompliance with requirements of this Order, 10 CFR Part 745, 45 CFR Part 46.

- (4) The appropriate HSP Program Manager shall be notified in writing immediately upon the appointment of a new DOE Site IRB Chair or DOE Site Institutional Official.
- e. Reporting. HSR projects shall be reported annually to the HSR Projects Database (HSRD) in accordance with directions and schedules provided by the HSP Program Manager.
- f. Protected Classes. Research involving fetuses, pregnant women, and in vitro fertilization; prisoners; or children shall be conducted in accordance with 45 CFR Part 46 Subparts B, C, and D.
- g. IRB Registration. Each IRB that is designated by an institution under an assurance of compliance approved for Federal-wide use by the Office for Human Research Protections (OHRP) under 45 CFR Part §46.103(a) and that reviews research involving human subjects conducted or supported by the Department of Health and Human Services (HHS) shall be registered with HHS in accordance with 45 CFR Part 46 Subpart E.

5. RESPONSIBILITIES.

All DOE employees, contractors, financial assistance recipients, and parties to other DOE agreements share the responsibility to protect the rights and welfare of human research subjects. The Secretary of Energy is responsible for oversight of the conduct of DOE-related human subject research.

- a. Under Secretary for Science.
 - (1) Monitors implementation of this Order, 10 CFR Part 745, and 45 CFR Part 46, within DOE in accordance with policy established by the Secretary and in consultation with the NNSA, as appropriate.
 - (2) Determines what constitutes Departmental-related HSR, in consultation with the NNSA.
 - (3) Ensures implementation of human research subject protection measures in accordance with the requirements of this Order, 10 CFR Part 745, and 45 CFR Part 46, in consultation with the NNSA.
 - (4) Designates the DOE Institutional Official. For DOE, the Institutional Official is the Associate Director for Biological and Environmental Research, Office of Science.
 - (5) Designates the DOE HSP Program Manager. For DOE, the HSP Program Manager resides within the Office of Science's Office of Biological and Environmental Research.

- (6) Delegates review and approval of statements of work for HTM projects submitted by DOE's non-NNSA sites to the HSP Program Manager.
- b. Under Secretary for Nuclear Security and Administrator of the National Nuclear Security Administration designates the NNSA HSP Program Manager and delegates review and approval of statements of work for HTM projects submitted by DOE's NNSA Sites to the NNSA HSP Program Manager. The NNSA HSP Program manager resides within the Office of the Senior Adviser for Environment, Safety, and Health.
 - c. The DOE Institutional Official is the Senior DOE Official, responsible for overseeing and monitoring Departmental implementation of the requirements of this Order, 10 CFR Part 745, and 45 CFR Part 46, in consultation with the NNSA, as appropriate. The DOE Institutional Official is also responsible for: 1) ensuring the Central DOE Institutional Review Board (IRB) complies with applicable Federal and DOE regulations; 2) ensuring the OHRP Federalwide Assurance (FWA) and IRB registration are properly maintained and current; and 3) formally appointing the Chair and the Vice Chair after selection by the Board. The Institutional Official must concur on all requests for partial or full exemptions from the requirements of this Order.
 - d. DOE HSP Program Manager.
 - (1) Develops procedures for the HSP program in consultation with the NNSA HSP Manager, as appropriate.
 - (2) Prepares and updates guidance to be followed for obtaining approval for HSR in consultation with the NNSA HSP Manager, as appropriate.
 - (3) Reviews/approves (or when an NNSA element is involved, reviews and may recommend approval of) local plans to correct any noncompliance or to mitigate adverse study events, ensuring they comply with applicable HSP requirements.
 - (4) Reviews and approves statements of work for HTM projects submitted by DOE's non-NNSA sites. Ensures compliance with DOE requirements [see paragraph 4.a.(2)], and, for Work for Others HTM projects, coordinates with appropriate Headquarters Work for Others leads prior to approving such statements of work for initiation. Ensures Site Offices and M&O contractors are aware of decisions concerning proposed HTM work.
 - (5) Provides advice and guidance on evolving Departmental and national bioethics and regulatory issues regarding human research subject protection and helps identify and resolve program/project concerns in consultation with the NNSA HSP Program Manager, as appropriate.

- (6) Develops and conducts educational programs on bioethics and human research subjects protection requirements, practices, and procedures relevant to DOE employees, DOE contractor personnel, financial assistance recipients, and the public in consultation with the NNSA HSP Program Manager, as appropriate.
 - (7) Regularly conducts institutional performance reviews to assess compliance with human research subject protection requirements in consultation with the NNSA HSP Program Manager, as appropriate.
 - (8) Serves as the Chair of the DOE Human Subjects Working Group and as official DOE representative to groups with bioethics and HSP interests. The NNSA HSP Program Manager shall be invited to attend all such meetings and to co-chair meetings, as appropriate.
 - (9) Makes recommendations to the Secretary, after concurrence from, and through the Institutional Official, regarding requests for exemptions from the requirements of this Order and satisfies the advance notice and publication requirements of 10 CFR Part 745.101(i) prior to the granting of any exemption (in consultation with the NNSA HSP Program Manager, as appropriate).
 - (10) Concurs on HSP provisions in interagency agreements, in consultation with the NNSA HSP Program Manager, as appropriate.
 - (11) Maintains the HSR Projects Database for DOE.
- e. NNSA HSP Program Manager.
- (1) When an NNSA element is involved, reviews requests for exemptions to requirements of this Order and makes recommendations to the Secretary through the NNSA Administrator after concurrence from the Institutional Official. Ensures that the advance notice and publication requirements of 10 CFR Part 745.101(i) are met prior to the granting of any exemption. Also reviews and approves statements of work for HTM projects submitted by NNSA sites. Ensures compliance with DOE/NNSA requirements and, for Work for Others HTM projects, coordinates with the NNSA Office of Institutional Programs prior to approving such projects for initiation. Ensures Site Offices and M&O Contractors are aware of decisions concerning proposed HTM work.
 - (2) Works with the DOE HSP Program Manager, as outlined in paragraph 5.

f. Office of Intelligence.

- (1) Reviews and approves, prior to initiation, statements of work for HTM projects received from members of the intelligence community.
- (2) Reviews and approves statements of work for non-HTM, intelligence-related HSR prior to initiation.
- (3) In these reviews, coordinates with the appropriate HSP Program Manager.

g. Secretarial Officers or their Designees.

- (1) Ensure that all proposals for research, studies, tests, surveys, surveillance, or other data collection are reviewed to identify research involving human subjects.
- (2) Ensure that any questions or uncertainties regarding the applicability of human research subjects protection requirements to such proposals, and any other issues and concerns regarding the requirements of this Order, are promptly referred to the appropriate HSP Program Manager for resolution.
- (3) Ensure that the contracting officer is advised when work statements for proposed agreements include HSR to ensure that the CRD or its requirements (as appropriate) will be applied to HSR conducted with DOE funding, at DOE institutions, or by DOE personnel under agreements other than site/facility management contracts, such as support services contracts, grants, cooperative agreements, work-for-others agreements, and interagency agreements.
- (4) Ensure that the contracting officer, after being notified of the affected contracts, incorporates the CRD into the affected contracts by way of the Department of Energy Acquisition Regulations (DEAR) Laws, regulations, and directives clauses included in those contracts. In the case of contracts or other agreements requiring contractor performance of activities covered by the CRD, but which do not contain the Laws, regulations, and DOE directives clause, the contracting officer will work to include the requirements as appropriate.
- (5) Ensure their staffs and field elements comply with the requirements of this Order, including the notification requirements in paragraph 4d.
- (6) Ensure relevant personnel actively participate in human research subjects protection training and educational programs.
- (7) Ensure that self-assessments are periodically conducted to verify compliance with the requirements of this Order.
- (8) At their discretion, conduct further review and approve or disapprove research that has been approved by the IRB. (Note: Secretarial Officers or

their designees may not approve HSR that has not been approved by an IRB. See 10 CFR Part 745.112.)

- (9) Ensure appropriate oversight of the administration of research subjects protection programs of contractors and financial assistance recipients under their cognizance, and other parties to DOE agreements, to ensure compliance with applicable human research subjects protection requirements.
- (10) Ensure that the HSP Program Manager and the NNSA HSP Manager are involved in negotiating those portions of interagency agreements that address HSR.
- (11) Appoint a point of contact for interacting with the appropriate HSP Program Manager on program-related and/or Department-wide issues.

h. DOE Site Offices.

- (1) Ensure contracts, financial assistance agreements, and other agreements involving HSR require compliance with the requirements set forth in the CRD associated with this Order (Attachment 1), 10 CFR Part 745, and 45 CFR Part 46.
- (2) Ensure that contractors establish and maintain a process for:
 - (a) Identifying and reporting HTM work according to DOE Policy and this Order;
 - (b) Notifying the HSP Program Manager(s) as required in paragraph 1 of the CRD; and
 - (c) Training relevant personnel in HSP requirements as required by paragraph 10 of the CRD.

6. REFERENCES.

- a. DOE O 206.1, *Department of Energy Privacy Program*, dated 1-16-09, which ensures compliance with privacy requirements;-establishes a Departmental training and awareness program for all DOE Federal and contractor employees to ensure personnel are cognizant of their responsibilities for safeguarding Personally Identifiable Information (PII) and complying with the Privacy Act; and provides Departmental oversight to ensure compliance.
- b. DOE O 241.1B, *Scientific and Technical Information Management*, dated 12-13-10, which establishes Department of Energy (DOE) requirements and responsibilities to ensure that scientific and technical information (STI) is identified, processed, disseminated, and preserved in a manner that (a) enables the scientific community and the public to locate and use the unclassified and

unlimited STI resulting from DOE's research and related endeavors and (b) ensures access to classified and unclassified controlled STI is protected according to legal or Departmental requirements.

- c. DOE O 412.1A, *Work Authorization System*, dated 4-21-05, which provides the policy, responsibilities, and procedures for authorizing and administering DOE-funded work performed under DOE contracts.
- d. DOE O 481.1C, *Work for Others (Non-Department of Energy Funded Work)*, dated 1-24-05, which establishes the policy, responsibilities, and procedures for authorizing and administering work for non-DOE entities by DOE/National Nuclear Security Administration (NNSA) and/or their respective contractor personnel or the use of DOE/NNSA facilities that is not directly funded by DOE appropriations.
- e. DOE M 481.1-1A Chg 1, *Reimbursable Work for Non-Federal Sponsors Process Manual*, dated 9-28-01, provides detailed requirements to supplement DOE O 481.1C, *Work For Others (Non-Department of Energy Funded Work)*, dated 1-24-05, which establishes requirements for the performance of work for non-DOE/non-NNSA entities by DOE/NNSA/contractor personnel and/or the use of DOE/NNSA facilities that is not directly funded by DOE/NNSA appropriations.
- f. DOE M 483.1-1, *DOE Cooperative Research and Development Agreements Manual*, dated 1-12-01, which provides detailed requirements to supplement DOE O 483.1, *DOE Cooperative Research and Development Agreements*, dated 1-12-01, which establishes requirements for the performance of technology transfer through the use of Cooperative Research and Development Agreements (CRADAs). DOE O 484.1, *Reimbursable Work for the Department of Homeland Security*, dated 8-17-06. The Order establishes DOE policies and procedures for the acceptance, performance, and administration of reimbursable work directly funded by the Department of Homeland Security.
- g. 10 CFR Part 600, DOE Financial Assistance Rules, which provides the policies and procedures for administration and management of all DOE financial assistance activities.
- h. 10 CFR Part 602, Epidemiology and Other Health Studies Financial Assistance Program, which sets forth the policies and procedures applicable to the award and administration of financial assistance agreements and cooperative agreements for health-related research, education/training, conferences, communication, and related activities.
- i. 10 CFR Part 605, Office of Science Financial Assistance Program, as explained at www.er.doe.gov/grants/605.asp, which provides policies and procedures for the administration and management of basic and applied research financial award agreements awarded by the Office of Science.

- j. 10 CFR Part 745, Protection of Human Subjects, which set Federal requirements for DOE for the protection of human subjects involved in research activities.
- k. 10 CFR Part 1008, Records Maintained on Individuals (Privacy Act) which establishes the procedures to implement the Privacy Act of 1974 (PL. 93-579, 5 U.S.C. 552a) within DOE of Energy.
- l. 45 CFR Part 46, Protection of Human Subjects, Subparts B, C, and D, which sets out DOE prescribed DHHS requirements for protected classes of human research subjects and Subpart E for IRB registration.
- m. The National Nuclear Security Administration Act, Title 32 of the National Defense Authorization Act for Fiscal Year 2000, Public Law No. 106-65; 50 USC 2401 et seq.
- n. The Freedom of Information Act, 5 USC Section 552, as amended, which establishes the right of citizens to request information from Federal agencies and establishes a framework of procedures to implement this right.
- o. Secretarial Policy Memo on Military or Intelligence-Related Human Subject Research, December 9, 2009, and related cover memo, February 18, 2010.
- p. DOE IRB Checklist for Reviewing Human Subjects Research Protocols that Utilize PII and DOE Checklist for Use by Researchers Conducting Human Subjects Research that Utilizes PII, Office of Biological and Environmental Research, 2009.

7. DEFINITIONS.

- a. Appropriate HSP Program Manager. The DOE HSP Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager).
- b. Assurance. The written documentation, satisfactory to the Secretary of Energy, required from the prospective performing institution, that ensures institutional compliance with and implementation of DOE and Department of Health and Human Services (DHHS) regulations for the protection of human research subjects. The only documentation currently meeting this requirement is a Federal-wide Assurance (FWA). See: http://www.hhs.gov/ohrp/assurances/assurances_index.html.
- c. Adverse Event. Any unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subjects participation in the research, whether or not considered related to the subject's participation in the research.
- d. De-identified Data. A data set that has no, or limited, identifiers and for which a person with current knowledge of generally accepted scientific principles

determines that the risk that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient, to identify an individual who is a subject of the information, has been reduced to the extent practicable. A graded approach must be used in balancing de-identification of the datasets and the usability of the dataset to accomplish the needed research.

- e. DOE Human Subjects Protection Program Manager (HSP Program Manager). The individual designated by the Under Secretary for Science to oversee the non-NNSA components of DOE's Human Subjects Protection Program.
- f. DOE Institutional Official. The Senior DOE Official responsible for overseeing and monitoring Departmental implementation of the requirements of 45 CFR Part 46, 10 CFR 745, *Protection of Human Subjects*, and this Order, in consultation with NNSA, as appropriate.
- g. DOE HSR Projects Database (HSRD). An unclassified compilation of summary information, which is available on the website at: <http://hsrd.ornl.gov/>, updated annually, on every non-exempt HSR project funded by DOE, conducted at DOE institutions or facilities, or performed with DOE or contractor personnel.
- h. Human Subjects Research (HSR). Any systematic investigation (including research development, testing, and evaluation) involving intervention or interaction with individuals or using their personally identifiable information or materials, designed to develop or contribute to generalizable knowledge.² In addition to traditional biomedical and clinical studies, such research includes but is not limited to studies that—
 - (1) use humans to examine devices, products, or materials with the express purpose of investigating human-machine interfaces or evaluating environmental alterations when humans are the subjects being tested;
 - (2) use personally identifiable bodily materials such as cells, blood, tissues, urine, or hair, even if the materials were collected previously for a purpose other than the current research;
 - (3) collect and use personally identifiable information such as genetic information or medical and exposure records, even if the information was collected previously for a purpose other than the current research;
 - (4) collect personally identifiable or non-identifiable data, surveys, or questionnaires through direct intervention or interaction with individuals; and

² New information that has relevance beyond the population or program from which it was collected or information that is added to the scientific literature.

- (5) search for generalizable knowledge about categories or classes of subjects (e.g., linking job conditions of worker populations to hazardous or adverse health outcomes).

Human subject research does not include the following:

- (1) studies to improve the safety or execution of procedures that apply to routine occupational activities;
 - (2) occupational health surveillance of DOE Federal or contractor employees to determine apparent departures from typical health status and not for the purpose of obtaining generalizable knowledge; and
 - (3) employee surveys used as management tools to improve worker or contractor performance as long as the identity of the participant is protected.
- i. Human Terrain Mapping. Research and data gathering activities primarily conducted for military or intelligence purposes to understand the “human terrain,”—the social, ethnographic, cultural, and political elements of the people among whom the U.S. Armed Forces are operating and/or in countries prone to political instability. This work includes observations, questionnaires, and interviews of groups of individuals, as well as modeling and analysis of collected data, and may become the basis for U.S. military actions in such locations. In addition to Human Terrain Mapping (HTM), such activities are often referred to as human social culture behavior (HSCB) and human terrain systems (HTS) studies. It is DOE policy that HTM activities will be managed as HSR.
 - j. HTM Data. Data collected or used as part of HTM efforts, as described above, as well as any auxiliary data on the same group(s) of individuals.
 - k. NNSA Human Subjects Protection Designee (NNSA HSP Program Manager). The individual appointed by the NNSA Administrator to oversee the Human Subjects Protection Program for NNSA elements.
 - l. Institution. Any public or private entity or agency (including Federal, State, and other agencies). This term refers to laboratories and other facilities managed by DOE, DOE contractors, or DOE financial assistance recipients.
 - m. Institutional Review Board (IRB). A committee or board established by an institution that performs initial and continuing reviews of research involving human subjects, and is registered with the Office for Human Research Protections (OHRP) and designated on an FWA.
 - n. Personally Identifiable Information. Any information collected or maintained about an individual, including but not limited to, education, financial transactions, medical history and criminal or employment history, and information that can be

used to distinguish or trace an individual's identity, such as his/her name, Social Security number, date and place of birth, mother's maiden name, biometric data, and any other personal information that is linked or linkable to a specific individual.

- o. Unanticipated Problem. In general, to be classified as an unanticipated problem, any incident, experience, or outcome should meet **all three** of the following criteria:
 - (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
 - (2) Related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
 - (3) Likely to place subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
 - p. Work for Others. Work for non-DOE entities by DOE/NNSA and/or their contractors or use of DOE/NNSA facilities for work that is not directly funded by DOE/NNSA appropriations.
 - q. Sponsor. An entity that provides work for others funding.
8. CONTACT. Questions regarding this Order should be addressed to the DOE Program Manager, HSP Program, Office of Science, Office of Biological and Environmental Research, telephone 301-903-3213, or the NNSA HSP Program Manager, as appropriate. Information about the DOE HSP protection program may be found at <http://humansubjects.energy.gov/>.

BY ORDER OF THE SECRETARY OF ENERGY:



DANIEL B. PONEMAN
Deputy Secretary

**CONTRACTOR REQUIREMENTS DOCUMENT
DOE O 443.1B, PROTECTION OF HUMAN SUBJECTS**

Regardless of the performer of the work, the contractor is responsible for compliance with the requirements of this Contractor Requirements Document (CRD).

The contractor is responsible for flowing down the requirements of this CRD to subcontracts at any tier to the extent necessary to ensure the contractor's compliance with the requirements.

Note: Throughout this CRD, the term "Human Subjects Protection Program Manager (HSP Program Manager)" refers either to the DOE HSP Program Manager or to the NNSA HSP Program Manager except where otherwise noted.

As directed by the contracting officer, the contractor shall—

1. Ensure notification of the HSP Program Manager (and, when an NNSA element is involved, the NNSA HSP Program Manager):
 - a. Prior to initiation of any new HSR project, even if it meets the regulatory definition of exempt HSR as outlined in 10 CFR Part 745.101(b), involving:
 - (1) an institution without an established Institutional Review Board (IRB);
 - (2) a foreign country;
 - (3) the potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);
 - (4) research subjects in a protected class (fetuses, pregnant women, and in vitro fertilization; prisoners; or children); or
 - (5) the generation or use of classified or unclassified controlled information.
 - b. Within 48 hours of the following, and, provide a description of corrective actions taken immediately following the incident, as well as corrective actions to be taken for concurrence by the appropriate HSP Program Manager:
 - (1) any significant adverse events, unanticipated problems, and complaints about the research,
 - (2) any suspension or termination of IRB approval of research;
 - (3) any significant non-compliance with HSP Program procedures or other requirements, which shall be reported to the IRB for evaluation for further action with the appropriate HSP Program Manager;
 - c. Immediately, of a finding of a suspected or confirmed data breach involving PII in printed or electronic form and to the DOE-Cyber Incident Response Capability

immediately, in accordance with the requirements of the CRD associated with DOE O 206.1, and provide a description of any corrective actions taken within 48 hours and a description of corrective actions to be taken for concurrence by the appropriate HSP Program Manager.

- d. Upon appointment of a new DOE Site IRB Chair or DOE Site Institutional Official.
2. Ensure that research involving human subjects, regardless of source of funding, is conducted in accordance with applicable requirements. (See 10 CFR Part 745 and 45 CFR Part 46).¹
 3. Ensure that contractor-issued solicitations or proposals for research, studies, tests, surveys, surveillance, or other data collection are reviewed to identify research involving human subjects and that any resulting agreements include the substance of the requirements in this CRD.
 4. Ensure that no research involving human subjects, regardless of funding source, is initiated without prior IRB approval under the terms of an approved assurance covering the research.
 5. Ensure that any Human Terrain Mapping (HTM) work complies with DOE requirements specified in this CRD, namely:
 - a. HTM projects, conducted with DOE funding, at DOE institutions (regardless of funding source), or by DOE contractor personnel (regardless of funding source or location of work conducted), whether done domestically or in an international environment, and including classified and proprietary research, shall be strictly limited to only those projects involving the analysis and modeling of de-identified data.
 - b. Documented process and procedures shall be developed to ensure that: 1) statements of work for HTM projects are submitted to the Site Office, for information, and to the appropriate HSP Program Manager (and when an NNSA element is involved, the NNSA HSP Program Manager), for DOE Headquarters review and approval, prior to initiation, and 2) relevant M&O personnel are trained in HTM requirements. If the project is to be conducted by or for the intelligence community, the Office of Intelligence must also review and approve it prior to project initiation. The HSP Program Manager(s) and the Office of Intelligence shall engage the recognized DOE site IRB and, if needed, the principal investigator (PI) and/or sponsor, in clarifying whether the proposed project is HTM, and if so, that the data to be used will be de-identified. Additionally, the PI will provide written verification that only de-identified data (as defined in paragraph 7d of this Order) will be used.

¹ Ensure that research is reviewed at intervals appropriate to the degree of risk, but not less than once per year, to assess the risk to test subjects and to assure the risk is reasonable in relation to anticipated benefits.

- c. For Headquarters approved projects, the recognized DOE site IRB is the only entity authorized to determine whether the HTM data received by the PI after project initiation meets DOE criteria for de-identification. If the DOE site does not have an internal IRB, the Central DOE IRB will be the responsible IRB.
 - d. If, in the case the sponsor requests assistance in the de-identification of HTM data prior to start of any work on the sponsor's project and/or re-identification of data following completion of the project, DOE sites may provide such services under a separate contract and/or task order with the sponsor by following the appropriate DOE standard operating procedure approved by the DOE Institutional Official, DOE Office of Science.²
6. Submit an application for a Federal-wide Assurance (FWA) to the Office of Human Research Protections (OHRP) with Department of Health and Human Services (DHHS) and, once approved by DHHS, maintain this FWA covering proposed and ongoing HSR and provide a copy to the appropriate HSP Program Manager. The Secretary of Energy uses the approved FWA as appropriate written documentation from DOE Sites committing to institutional compliance with and implementation of DOE and DHHS regulations for the protection of human research subjects. See http://www.hhs.gov/ohrp/assurances/assurances_index.html and/or contact the DOE HSP Program Manager, Office of Science, Office of Biological and Environmental Research, telephone 301-903-3213, or the NNSA HSP Program Manager, as appropriate.
 7. Periodically conduct self-assessments to ensure compliance with the HSP Program procedures and other requirements.
 8. Prepare and submit an annual report for the HSR Projects Database in accordance with directions and schedules provided by the appropriate HSP Program Manager.
 9. Submit requests for exemptions from these requirements in writing through the contracting officer to the appropriate HSP Program Manager.
 10. Ensure relevant personnel actively participate in HSP training and educational programs.

² It should be noted that: a) only limited communications, if needed, may take place between the organization de-identifying and/or re-identifying the sponsor's data and the organization performing work on the sponsor's task; b) the identified data set shall not be shared with the individual who will perform work on the sponsor's task; and c) the de-identified dataset shall be sent directly by the sponsor to the individual performing work on the sponsor's task and not by the organization at the DOE site that de-identified it.