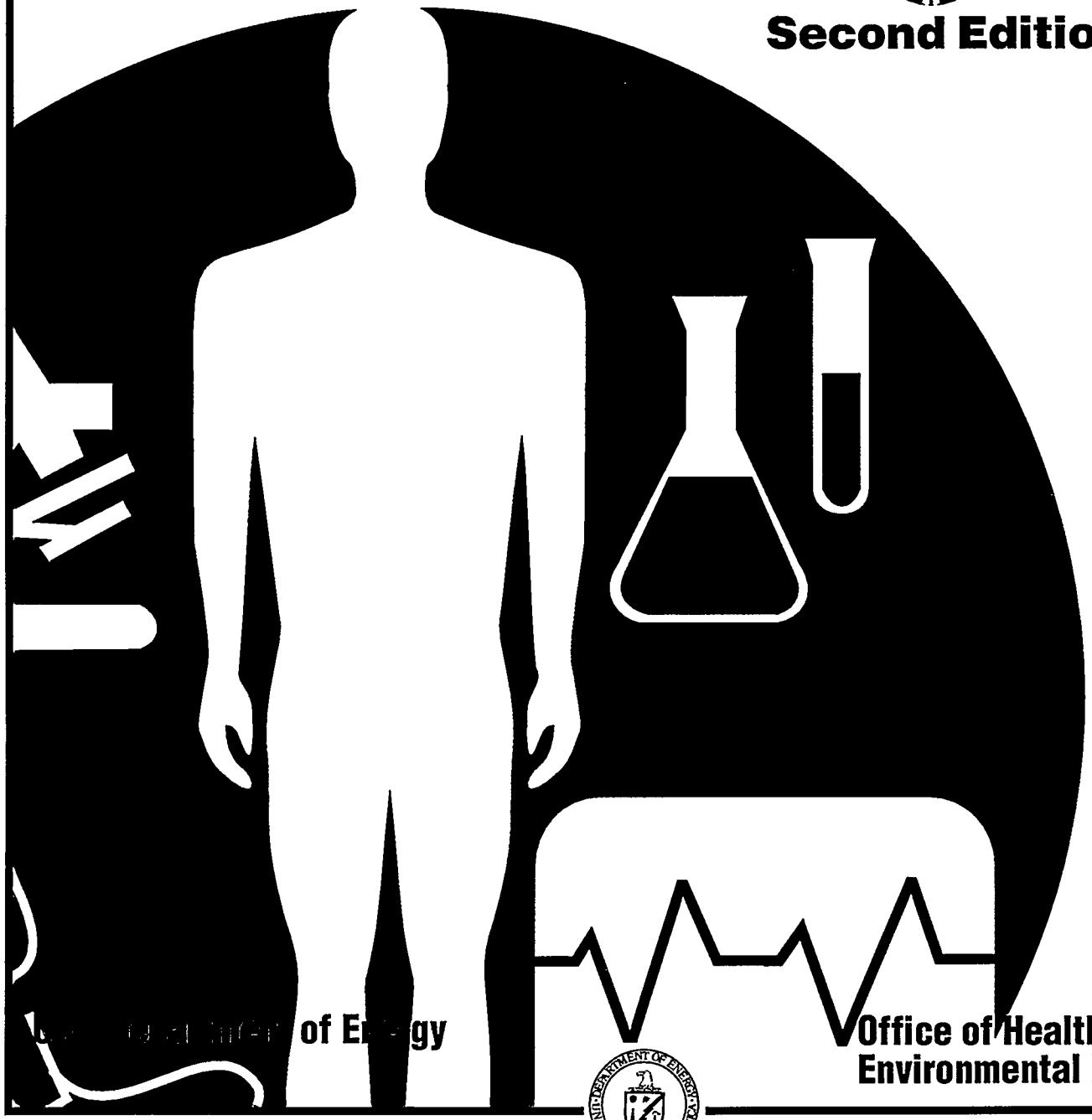
PROTECTING HUMAN RESEARCH SUBJECTS

HUMAN SUBJECTS RESEARCH HANDBOOK

Second Edition



U.S. Department of Energy

Office of Health and Environmental Research

The Secretary of Energy
Washington, DC 20585

January 30, 1996

MEMORANDUM FOR: ALL DEPARTMENTAL EMPLOYEES

FROM: HAZEL R. O'LEARY

SUBJECT: Revised Human Subject Handbook

Research on humans performed in accordance with ethical and humanitarian principles allows the experiments to be performed that provide medical and scientific benefits to individuals and to the Nation. Medical trials led to the development of the polio vaccine. Radiation research brought us treatments for cancer and X-rays to pinpoint medical problems. It is important to remember that many lives have been saved and many more will be saved using diagnoses and treatments of diseases derived through medical trials.

To assure that human subjects are fully protected from potential abuses in research experimentation, Federal regulations have been promulgated. It is the policy of the Department that the rights and welfare of human subjects involved in research supported or sanctioned by the Department of Energy be protected in accordance with 10 CFR Part 745 (Federal Policy for the Protection of Human Subjects); and, until the requirements of the Department policies and orders have been met, no new research activity involving human subjects shall be initiated.

A Human Subjects Handbook was distributed by the Office of Energy Research to provide guidance in the implementation of these regulations and a single resource for all of the basic reference information users may need. This newly revised version (spring 1995) has been prepared to provide broader and more current information. It includes a more comprehensive and definitive description of the roles and responsibilities of each participant in the preparation and approval process for research involving human subjects. The presentation of research project assurances has been expanded and clarified. The format, organization of material, text layout, and graphics in the Handbook have been upgraded. Numerous tables and charts have been added for enhanced understanding and interpretation of data. An expanded glossary of terms, table of contents, and subject index have been added; and, lastly, special topics of currently significant importance have been introduced.

The issuance and distribution of this Handbook serves as a reminder of the importance with which the Department views this topic and the leadership we have taken in overseeing the proper implementation of contemporary research ethics, rules, and regulations by our programs, laboratories, and field offices.

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Human Subjects Research Handbook

Second Edition

U.S. Department of Energy
Office of Health and Environmental Research

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Many of the materials and resources included in this handbook were collected from various human subjects research meetings and conferences, DOE laboratory resource manuals, and from other resources such as the OPRR *1993 Protecting Human Subjects Institutional Review Board Guidebook* and the Food and Drug Administration Information Sheets for Institutional Review Boards and Clinical Investigators.

Foreword

Purpose of This Handbook

This handbook serves as a guide to understanding and implementing the Federal regulations and U.S. Department of Energy (DOE) Orders established to protect human research subjects. The first edition of this handbook was published in 1992, shortly after DOE and 15 other Federal agencies and departments formally adopted the Common Rule for the protection of human subjects in 1991. This revised edition incorporates many of the resources and instructional materials included in the first edition while addressing current issues and concerns in the human research arena.

Material in the handbook is directed toward new and continuing institutional review board (IRB) members, researchers, institutional administrators, DOE officials, and others who may be involved or interested in human subjects research. It offers a comprehensive overview of the various requirements, procedures, and issues relating to human subjects research today. All DOE program offices and institutions that are involved in human subjects research should make this handbook an available resource at their office/facility.

A Brief History of the Ethical Guidelines That Govern the Human Subjects Protection System

The principles that underlie human subjects protections today are found in three main documents—the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report.[1]

The Nuremberg Code was developed in the late 1940s for the Nuremberg military tribunal as standards by which to judge human experimentation conducted by the Nazis. The code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects: voluntary consent, minimization of risk and harm, favorable risk to benefit ratio, qualified researchers using appropriate research design, and freedom of the subject to withdraw at any time.

The Declaration of Helsinki, prepared by the World Medical Association in 1964 and revised in 1975 and 1989, endorses principles similar to those in the Nuremberg Code and distinguishes therapeutic from nontherapeutic research.

[1] Reprints of these documents are included in the appendix (Chapter 15) of this handbook.

The Belmont Report was published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. This report identifies three essential requirements for the ethical conduct of research involving human subjects: respect for persons, beneficence, and justice.

Respect for persons requires true informed consent, which entails dissemination of clear and adequate information about the research to the research subjects, full comprehension by participating subjects, and true voluntariness, which occurs when agreement to participate is free from coercion and undue influence. *Beneficence* includes the consideration of all possible harms, not just physical or psychological pain or injury. It suggests that consideration of possible benefits should involve not only the benefits to the individual, but also the societal benefits that might be gained from the research. *Justice* mandates that the selection of research subjects be the result of fair selection procedures and also result in fair selection outcomes. It further indicates that researchers must follow 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 only in certain conditions, if at all.

> ***Respect for Persons***—*A recognition of the personal dignity and autonomy of individuals and special protection for those persons with diminished autonomy.*
>
> ***Beneficence***—*An obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.*
>
> ***Justice***—*Fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.*

The Nuremberg Code, the Declaration of Helsinki, and the Belmont Report served as the cornerstone for the drafting of the Federal Policy for the Protection of Human Subjects (known as the Common Rule). The Common Rule was adopted by 16 Federal agencies that conduct, support, or otherwise regulate human subjects research. DOE adopted the Common Rule as Title 10 Code of Federal Regulations (CFR), Part 745. *(See Chapter 2 for a copy of this regulation.)* What follows in this handbook is a series of chapters that provide comprehensive guidance for complying with the requirements found in Federal regulations and associated DOE Orders for protection of human subjects.

How to Use the Handbook

This handbook is divided into three parts: procedures and responsibilities, special topics, and resources. Part 1 of the handbook (Chapters 1-6) provides an overview and general guidance concerning research involving human subjects. It gives direction on how to identify human subjects research and provides reprints of the Federal regulations and DOE orders established to protect human research subjects. These chapters detail the roles and responsibilities of the various entities—DOE program managers, field offices, laboratory administrators, institutional review boards, and investigators—that may be involved in human research processes and procedures.

Part 2 of the handbook (Chapters 7-13) addresses special topics or issues regarding current human subject research. It includes guidance in cases where research projects involve classified or sensitive data or when research sponsors have proprietary concerns. It provides information on the use of

personally identifiable human subjects data and general guidance on cooperative research projects including projects involving international collaborators. Additionally, Part II of the handbook covers issues such as the difference between occupational health surveillance and human subjects research, the reporting of adverse events, compensation for injury, research involving vulnerable populations, and various other significant issues that IRBs and others involved in human research must address. Toward the end of Part II, there is information on DOE's performance review system and on audit systems established at other Federal agencies. Checklists are provided to help institutions evaluate their compliance with the Common Rule. Also included is a description of the purpose of the DOE Human Subjects Research Projects Database and the way to access it on the Internet, as well as the availability of various educational materials on the protection of human subjects developed by DOE's Office of Health and Environmental Research (OHER).

Part 3 of the handbook (Chapters 14-17) consists of reference chapters, including an appendix, a list of DOE and other Federal agency contacts, a glossary, and a list of additional resources on human research topics that handbook users may find valuable for in-depth review of topics of special interest.

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Acronyms and Abbreviations

The following is a list of acronyms and abbreviations that appear in this handbook or that are in some way associated with human subjects research at the Department of Energy.

ADAMHA	Alcohol, Drug Abuse and Mental Health Administration
ANL	Argonne National Laboratory
ARENA	Applied Research Ethics National Association
BAA	Broad Agency Announcement
BNCT	Boron Neutron Capture Therapy
BNL	Brookhaven National Laboratory
CAT	Computerized Axial Tomography
CCMI	Colorado Consortium of Medical Institutes
CDC	Centers for Disease Control and Prevention
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CPA	Cooperative Project Assurance
CPRP	Cooperative Protocol Research Program
CRADA	Cooperative Research and Development Agreement
DEAR	Department of Energy Acquisition Regulations
DHEW (DHHS)	Department of Health, Education, and Welfare (Department of Health and Human Services)
DHHS	Department of Health and Human Services
DOE	Department of Energy
DOJ	Department of Justice
DP	Defense Programs
DSMB	Data and Safety Monitoring Board
EE	Energy Efficiency and Renewable Energy
EH	Environment, Safety and Health
EIA	Energy Information Administration
EM	Environmental Management
EML	Environmental Measurements Laboratory
EPA	Environmental Protection Agency
ER	Energy Research

FACA	Federal Advisory Committee Act
FAR	Federal Acquisition Regulation
FDA	Food and Drug Administration
FE	Fossil Energy
FERMILAB	Fermi National Accelerator Laboratory
FFRDC	Federally Funded Research and Development Center
FOIA	Freedom of Information Act
FR	Federal Register
FTP	Field Task Proposal
FWP	Field Work Proposal
FY	Fiscal Year
GC	General Counsel
GOGO	Government Owned Government Operated
GPP	General Plan Project
HCO	Head of Contracting Organization
HEHF	Hanford Environmental Health Foundation
HERAC	Health and Environmental Research Advisory Committee
HQs	Headquarters
HR	Human Resources
HSB	Human Studies Board
IDE	Investigational Device Exemption
IG	Inspector General
IND	Investigational New Drug or Device
INEL	Idaho National Engineering Laboratory
IPA	Intergovernmental Personnel Act
IRB	Institutional Review Board
ITRI	Inhalation Toxicology Research Institute
JAMA	Journal of American Medical Association
LANL	Los Alamos National Laboratory
LBL	Lawrence Berkeley Laboratory
LDRD	Laboratory Directed Research Development (funds)
LLNL	Lawrence Livermore National Laboratory
LM	Laboratory Management
M&O	Management and Operating contract
MDA	Medical Device Amendments
MPA	Multiple Project Assurance
MPBB	Maximum Possible Body Burden
MRI	Magnetic Resonance Imaging
NASA	National Aeronautics and Space Administration
NBAC	National Bioethics Advisory Commission
NCI	National Cancer Institute
NCTTA	National Competitiveness Technology Transfer Act

NDA	New Drug Application
NE	Nuclear Energy
NIH	National Institutes of Health
NIJ(DOJ)	National Institutes of Justice (Department of Justice)
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
NRC	Nuclear Regulatory Commission
NREL	National Renewable Energy Laboratory
OD	Office of Declassification
OHER	Office of Health and Environmental Research, DOE
OPRR	Office for Protection from Research Risks, NIH
ORA	Office of Research Administration
ORISE	Oak Ridge Institute for Science and Education
ORNL	Oak Ridge National Laboratory
PBI	Partial Body Irradiation
PHS	Public Health Service, DHHS
PI	Principal Investigator
PMA	Pharmaceutical Manufacturers Association
PNL	Pacific Northwest Laboratories
POC	Point of Contact
PPPL	Princeton Plasma Physics Laboratory
PRDA	Program Research and Development Announcement
PRIM&R	Public Responsibility in Medicine and Research
PSO	Program Secretarial Officer
R&D	Research and Development
RDRC	Radioactive Drug Research Committee
REM	Roentgen Equivalent in Man
RFP/RFA	Request for Proposal/Request for Award
RW	Radioactive Waste
SAMHSA	Substance Abuse and Mental Health Services Administration
SLAC	Stanford Linear Accelerator Center
SNL	Sandia National Laboratories
SPA	Single Project Assurance
SSRL	Stanford Synchrotron Radiation Laboratory
TBI	Total Body Irradiation
UCLA	University of California, Los Angeles
UCSF	University of California, San Francisco
WFO	Work for Others
WWW	World Wide Web

Protecting Human Research Subjects Within the Department of Energy

A. Introduction

This chapter emphasizes the importance of recognizing when research involves human subjects and gives an overview of how the U.S. Department of Energy (DOE) implements the Federal regulations and DOE orders designed to protect human subjects.

Reference Material Included In This Chapter

- Matrix of Roles and Responsibilities (Figure 1a).

The Federal Policy for the Protection of Human Subjects is called the Common Rule. For DOE, it is codified in Title 10 Code of Federal Regulations, Part 745 (10 CFR 745). (For the Department of Health and Human Services, the Common Rule is found at 45 CFR 46.) The primary DOE authority for protection of human subjects is DOE Order 1300.3, *Policy on the Protection of Human Subjects.* DOE Order 4300.2C, *Work for Others,* also governs protection of human subjects in research that is conducted by DOE or in DOE facilities, but is funded by sources other than DOE. *(See Chapter 2 for the full text of these regulations and orders.)*

Section B calls attention to the wide variety of research that may involve use of human subjects—a much broader range than some principal investigators and program managers realize. All of this research must be reviewed and approved as protecting human subjects by an institutional review board (IRB). This section also discusses the types of research that are or may be exempt from the requirement for IRB approval. It is not always easy to determine whether research is exempt from this requirement. Principal investigators (PIs) are urged to consult their IRBs. IRBs are encouraged to consult each other. Anyone is welcome to consult the informational contacts listed in Chapter 14.

Section C of this chapter surveys the roles and responsibilities of everyone charged by DOE with protection of human subjects, from the Associate Director of Health and Environmental Research to PIs. At the end of the chapter, a matrix summarizes each set of roles and responsibilities *(Figure 1a). (More details on the specific roles and responsibilities can be found in Chapters 3–6.)*

B. Identifying Human Subjects Research

> ***Research***—*A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.*
>
> ***Human Subject***—*A living individual about whom an investigator (whether professional or student) conducting research obtains—*
>
> - *Data through intervention or interaction with the individual.*
> - *Identifiable private information.*

Early in the process of developing a research project or protocol, investigators and program managers should identify whether it will involve human subjects. Human subjects research includes a broader range of research than many investigators and program managers realize. In addition to traditional biomedical and clinical studies, human subjects research includes studies that—

- Use humans **to test devices or products** or materials that have been developed through research. Also included is research that uses humans to examine human-machine interfaces.

- Use **data collected through intervention or interaction** with individuals. Intervention includes not only physical procedures (like drawing blood) but also manipulation of a subject's environment. Interaction includes interpersonal contact and other kinds of communication.

- Use **private information** that can be readily identified with individuals, even if the information was not collected specifically for the study in question. Information is private if the individual can reasonably expect it not to be made public or if the information concerns behavior that the individual can reasonably expect not to be observed or recorded.

- Use **bodily materials** such as cells, blood, urine, tissues, organs, hair, and nail clippings *even if the researcher did not collect these materials.* (Such research may be considered exempt from human subjects requirements if materials are unidentifiable. In all cases, the researcher should consult the institutional review board.)

- Use humans **to evaluate environmental alterations**—for example, weatherization options or habitat modifications.

Review of Research Involving Human Subjects

Before human subjects participate in research, 10 CFR Part 745 requires the project or protocol to be reviewed and approved by an IRB to determine whether or not subjects are at risk and, if so, whether the risk is acceptable. Risk is defined as exposure to the possibility of harm—whether physical, psychological, sociological, or other—as a result of participating in a research activity. Research means a systematic investigation, including pilot studies, designed to contribute to generalizable knowledge.

Research involves human subjects and requires such review and approval when—

- Human beings are asked to participate physically in an activity or to donate their tissues, organs, fluids, and/or other bodily materials.

- Information is sought from human beings directly (for example, through an interview or questionnaire) or indirectly (for example, through observation).

- Information concerning specific individually identifiable human beings is requested from third parties—whether through access to files, data banks, or other information repositories or through direct inquiry by third parties concerning the individuals in question.

Also, collaborative studies, in which materials or information are collected at another institution and sent to researchers at a DOE laboratory for study, require review and approval. Projects in which the investigator is the only subject require review and approval.

Research Activities That May Be Exempt From IRB Review

Research activities are exempt from the requirement for IRB approval when IRB review of proposed research indicates that research does not involve human subjects as defined in 10 CFR 745 and/or the only involvement of human subjects is in one of the categories listed under 10 CFR 745 Sec. 101(b)(1)-(6) (e.g., educational tests, taste and food quality evaluation, observation of public behavior). *(A complete list of the exemptions is provided in Chapter 5, along with further guidance on this subject.)* Human subjects regulations do not apply to exempt projects. Any research project involving human subjects that is thought to be exempt must be submitted to the IRB for a determination of exempt status.

Important: Institutions that have DHHS-approved assurances on file must abide by provisions of 45 CFR 46, Subparts A–D. Under these provisions, exemptions do not apply to research involving pregnant women, fetuses, human in vitro fertilization, or prisoners. Further, research involving children does not qualify either for the survey/interview exemption or for the observation of public behavior exemption except when the investigator does not participate in activities being observed.

In addition to the exemptions in 10 CFR 745, DOE has identified several other categories which may be exempt from protection of human subjects requirements. These include—

- Studies to improve the safety of routine procedures which apply to the conduct of normal day-to-day occupational activities.

- Occupational health surveillance of DOE employees and DOE contractor workers to determine apparent departures from typical health status. These are operational activities consistent with the comprehensive occupational health program of DOE, and it is the policy of DOE's Office of Health Studies that routine health surveillance and quick response candidate episode investigations are a part of the office's occupational health activities. Health surveillance activities as described do not constitute research as it is defined in 10 CFR 745; therefore, formal IRB review is not required. However, it is recommended that

the relevant IRB committees be made cognizant of these activities as part of the process of information dissemination. *(For more information on occupational health surveillance, see Chapter 10.)*

- Employee surveys used as management tools to improve worker or contractor performance are not considered to be research as defined by 10 CFR 745 so long as the identity of the participant is protected.

It is not always easy to determine which research activities require IRB review and approval and which are exempt. Human subjects research per se does not always mean the active accumulation of data or specimens from humans. For example, humans may participate in a study to test a specific device or piece of equipment. Although the human participant may not be the focus of the study, investigators must carefully consider the scope of the participant's involvement and any risks to which the subject may be exposed. It is also important to consider whether the activity (and associated risks) in which the subject is participating is part of the regular routine of the individual—something the participant would typically do or be involved in—or if the activity introduces risks that the participant would not normally encounter in his/her regular routine or occupation. Each project or protocol must be considered on a case-by-case basis, and the final determination should rest with the institutional IRB. It is therefore recommended that investigators consult with their institutional representative, their IRB chairperson, or one of the informational contacts listed in Chapter 14. IRBs are also encouraged to consult with each other and with DOE Headquarters.

C. Roles and Responsibilities

This section briefly describes the roles and responsibilities of each participant in the review and approval process for research involving human subjects. *(More detailed descriptions of the roles and responsibilities of the institution, the IRB, and the principal investigator are found in Chapters 3, 5, and 6 respectively.)* This section begins with the responsibilities of DOE Headquarters and field elements. The responsibilities of the performing institution are then described. These include preparation of a written assurance of compliance with the requirements set forth in 10 CFR 745 and the establishment and support of one or more IRBs. *(Additional detail on the establishment of IRBs is provided in Chapter 3 of this handbook.)* The responsibilities, membership, and procedures for local IRBs are set forth next. The section then offers guidance to the principal investigator (PI) in the preparation of protocols and consent forms and in the submission of proposal review packages to the local institutional review board (IRB). Also included are the requirements for the PI to notify the local IRB institutional management and DOE. All requirements for these steps must be satisfied before human subjects become involved in research. Finally, the entire review process is summarized in a matrix of responsibilities.

Applicability

The roles and responsibilities described in this chapter apply to any research involving human subjects funded by DOE, conducted in DOE facilities, or performed by DOE personnel. They apply to research supported by any funding source and to all types of research, including those listed in the following table.

Applicable Types of Funding Sources	
Cooperative Research and Development Agreements (CRADAs) Field Work Proposals Interagency Agreements Interlaboratory Transfers Laboratory Directed Research Development Funds Pilot Projects	Program Grants Research Grants Special Research Grants Thesis Research User Facility Agreements Work for Others

When in doubt, contact your institution's Office of Research Administration (ORA) or your institutional human subjects point of contact. (See *Informational Contacts, Chapter 14.)* If you need further assistance, contact DOE's Office of Health and Environmental Research at 19901 Germantown Road, Germantown, MD 20874-1290, Tel: (301) 903-5037, Fax: (301) 903-8521, E-mail: human.subjects-info@oer.doe.gov.

U.S. Department of Energy

Responsibility for the protection of human subjects at the Department of Energy has been delegated to the Office of Energy Research. Day-to-day responsibilities for this policy have been delegated to the Office of Health and Environmental Research (OHER). OHER implemented the first regulations for protection of human subjects in 1976 under the DOE predecessor agency, and these were adhered to until 1991, when, on June 18, the Common Rule was signed into law.

Associate Director for Health and Environmental Research, Department of Energy

The Associate Director for Health and Environmental Research (ER-70) or a designee—

- Develops and implements procedures for the protection of human subjects.
- Prepares and updates guidance to be followed for obtaining approval for human subject research.
- Approves all Single Project Assurances (SPAs) and oversees all negotiations and evaluation processes. ER-70 may delegate authority for evaluation and negotiation processes to the heads of field organizations.
- Reviews all research involving human subjects from SPA institutions for compliance with DOE regulations and orders and applicable Federal regulations. In a timely fashion, approves, rejects, or requests additional information on proposed work and provides written determination of human subjects compliance to the Program Secretarial Officer (PSO), appropriate head of the field organization, or directly to the performing institution.
- Investigates allegations of noncompliance with 10 CFR 745 and DOE orders, and recommends any appropriate action required to the PSO, head of the field organization, or directly to the performing institution.
- Facilitates interactions with other Federal agencies and departments. Serves as the official DOE representative on the Interagency Human Subjects Coordinating Committee.
- Convenes DOE-wide human subjects workshops.
- Coordinates the production and distribution of educational materials (such as newsletters, brochures, posters, the handbook, and the research projects database) to increase awareness of human subjects policies and procedures.
- Performs periodic reviews of procedures for implementing 10 CFR 745.
- Develops and maintains a database of current human subject research funded by DOE, performed at DOE facilities, or conducted by DOE personnel.

Program Secretarial Officers (PSOs) or Their Designees[1]

PSOs or their designees—

- Implement the procedures established by ER-70.

[1]Refer to Chapter 14, Informational Contacts, for a list of program office designees.

- Review all proposals and applications to identify research involving human subjects. (*See DOE Order 1300.3 paragraph 7f in Chapter 2.*)

- In accordance with procedures developed by ER-70, request determination of compliance by ER-70.

- Supply ER-70's determination of compliance with 10 CFR 745 to the cognizant contracting officer.

- Promptly notify ER-70 of adverse events and issues of noncompliance with 10 CFR Part 745.

NOTE: Because institutions that hold Multiple Project Assurances (MPAs) are not required to interact with PSOs or their designees on a project-by-project basis, they bear the primary responsibility in most cases for the PSO activities above.

Heads of Field Offices or Their Designees

Field office heads or their designees—

- Fulfill the responsibilities of PSOs under paragraph 7d in DOE Order 1300.3 for non-DOE funded work (primarily work-for-others projects) at DOE-owned or leased facilities.

- Fulfill the responsibilities of PSOs under paragraph 7d in DOE Order 1300.3 for DOE-funded work originating in the field office or Government-owned Government-operated facilities.

- Include—in appropriate solicitations—documentation of approval of human subjects research in accordance with 10 CFR 745. This documentation conforms to the requirements of paragraph 8 in DOE Order 1300.3.

- For institutions holding an SPA, receives completed assurance, certification, and ER-70 human subjects approval documents prior to initiation of research involving human subjects. For institutions holding an MPA, receives the institutional assurance number instead of the complete assurance.

Cognizant Contracting Officers (as stated in DOE Order 1300.3)

Cognizant contracting officers—

- Include in appropriate solicitations a provision requiring human subject research information in accordance with 10 CFR 745.

- Require receipt of complete assurance, certification, and ER-70 human subject approval documents prior to initiation of research involving human subjects.

DOE Institutions or DOE Contractor Institutions Conducting Human Research

Institutional administrators—

- Implement the procedures established by ER-70.
- Prepare assurance of compliance with 10 CFR 745 or 45 CFR 46 as applicable. (To obtain MPAs from the Department of Health and Human Services, institutions must provide assurance of compliance with 45 CFR 46, rather than 10 CFR 745.)
- Establish an institutional review board (IRB).
- Provide written authority to the IRB to approve, disapprove, or modify research proposals.
- Conduct continuing review, observe and verify changes, and monitor the conduct of research protocols.
- Assure compliance with IRB decisions and suspend or terminate approval of research projects when appropriate.
- Formally, appoint an IRB Administrator or an ORA and charge that individual or office with the responsibility as serving as the human subjects point of contact.
- Conduct periodic self assessment to assure institutional compliance with DOE orders and Federal regulations.

Institutional Review Boards (IRBs)—

- Establish procedures consistent with Federal regulations and DOE orders.
- Establish procedures for submission and review of research projects.
- Determine whether research projects require full board review, qualify for expedited review, or are exempt from the requirement for IRB approval.
- Conduct reviews of continuing research projects at least once a year and serve as a point of contact for investigators in need of guidance.
- Conduct periodic self-assessments of IRB's compliance with Federal regulations and DOE orders.

Authority of IRB With Respect to Research Projects Involving Human Subjects

- Approve, disapprove, or modify.
- Conduct continuing review.
- Observe/verify changes.
- Suspend or terminate approval.

Principal Investigator (PI)—

- Understands and has a copy of institution's assurance of compliance.
- Defines and documents research protocol, develops consent form, and prepares package for IRB review in consultation with a department chair, program manager, or other institutional authority, where appropriate.
- Obtains approval of the research's scientific merit and submits package to IRB for review.
- Modifies proposal or consent form as required by IRB or DOE.
- Obtains informed consent prior to any involvement of human subjects; follows approved procedures or requests IRB approval of changes; reports any injury, unexpected adverse events, unanticipated problems, or noncompliance with assurance; requests continuation of approval for continuing research.

Figure 1a. Matrix of Roles and Responsibilities

Project Tasks	DOE Hqs.	Inst. Official	IRB	IRB Chair	ORA	IRB Admin.	PI's Mgr.	PI
Propose to use humans as research subjects							X	X
Agree on type of IRB review needed (i.e., exempt, expedited, or full review)				X	X		X	X
Prepare proposal review package								X
Obtain scientific merit approval for proposal							X	X
Submit proposal package to IRB for review								X
Certify proposal is exempt from review				X	X			
Perform expedited reviews				X				
Convene IRB meetings				X		X		
Perform full IRB reviews			X	X				
Modify proposal and/or consent form as required by IRB or DOE								X
Signify IRB approval				X				
SPA only: Certify institutional approval		X						
Transmit SPA package to DOE					X	X		
Approve SPA package	X							
Notify PI of approval						X		
Send approved proposal for funding approval or start if already funded								X
Obtain informed consent prior to any involvement of human volunteers								X
Follow approved procedures or request IRB approval of changes								X
Report any injury, unexpected adverse event, unanticipated problem, or noncompliance with assurance				X	X			X
Request continuation of approval for continuing research								X
Perform annual reviews of approved human research			X	X				
Provide annual status report to DOE HQs					X	X		X
Provide guidance and education to staff and management					X	X		
Present IRB briefings or training as needed					X	X		
Maintain paperwork flow to PIs, institutional officials, and DOE					X	X		
Maintain written IRB procedures and update as needed					X	X		
Retain IRB records as required					X	X		
Retain signed consent forms and research records as required								X
Produce IRB records/forms as needed to support human protection audits					X	X		X

NOTE: Local circumstances may dictate using one choice rather than another (e.g., IRB Administrator rather than the ORA).

Applicable Federal Rules and U.S. Department of Energy Orders

A. Introduction

This section contains the legislative authorities in the Code of Federal Regulations (CFR) and U.S. Department of Energy (DOE) implementing orders that govern how human subjects research activities at DOE are to be carried out. The full text of each item described below follows (Sections B–F of this chapter) in order of description.

10 CFR Part 745, *Federal Policy for the Protection of Human Subjects; Notices and Rules (known as the Common Rule)*
A Common Rule for all agencies was promulgated to ensure uniform policies for the protection of human research subjects. The Common Rule was codified by DOE as 10 CFR Part 745, *Federal Policy for the Protection of Human Subjects; Notices and Rules.* It was officially adopted by DOE and 15 other Federal agencies and departments on June 18, 1991.

DOE Order 1300.3, *Policy on the Protection of Human Subjects*
While awaiting adoption of 10 CFR Part 745 by all Federal agencies, DOE published Order 1300.3 on August 23, 1990, to speed the Department's compliance with the Common Rule and to establish responsibility within DOE for implementing the rule's policies. The Order principally lays out the responsibilities and authorities of all DOE elements with respect to human subjects involved in research supported or sanctioned by DOE or conducted in DOE facilities.

DOE Order 4300.2C, *Work for Others (Non-Department of Energy Funded Work)*
DOE Order 4300.2C was revised on December 28, 1994, to specify contractual requirements that apply to work for others. The Order establishes the authority and responsibility of field elements and the Associate Director, Office of Health and Environmental Research (ER-70), for compliance with 10 CFR Part 745 and DOE Order 1300.3.

45 CFR 46, Subparts B, C, and D, Department of Health and Human Services, Protection of Human Subjects

45 CFR 46, Subparts B, C, and D, were promulgated by the U.S. Department of Health and Human Services (DHHS). These Subparts describe additional protection for human research subjects whom DHHS identified as vulnerable populations. Subpart B describes additional steps to protect fetuses, pregnant women, and human in vitro fertilization. Subpart C describes additional steps to protect prisoners when they are subjects of biomedical and behavioral research, and Subpart D describes additional steps to protect children who are subjects of research. Although none of these have been officially included yet within 10 CFR Part 745, *it is highly recommended that they be followed by DOE investigators.* For this reason, they are included in this chapter. Currently, DHHS is revising Subpart B. Once these revisions have been completed, it is DOE's intention to consider adoption of this subpart. *(For further guidance on vulnerable populations, see Chapter 11.)*

45 CFR 46, Research Activities Which May Be Reviewed Through Expedited Review Procedures

DHHS published a list of research activities that may be reviewed by the IRB through an expedited review process. 10 CFR 745.110 states that an IRB may use the expedited review procedure to review either or both of the following:

- Some or all of the research appearing on the DHHS list and found by the reviewer(s) to involve no more than minimal risk.
- Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

(For more information on expedited review procedures, see Chapter 5.)

Food and Drug Administration (FDA) Regulations and Policies

FDA has concurred in the Common Rule, but has not adopted the Policy in its entirety. Instead, FDA has made selected changes to its IRB and informed consent regulations that correspond to the Federal Policy. [*See Federal Register* 56 (June 18, 1991): 28025-28029.] FDA regulations pertaining to human subjects research are codified at 21 CFR 50 [Protection of Human Subjects (containing the informed consent requirements)] and 21 CFR 56 (Institutional Review Boards). These regulations are not included in this handbook.

Applicability of FDA Regulations

- Clinical investigations.
- Regulated products—drugs, devices, biologics, food/color additives.

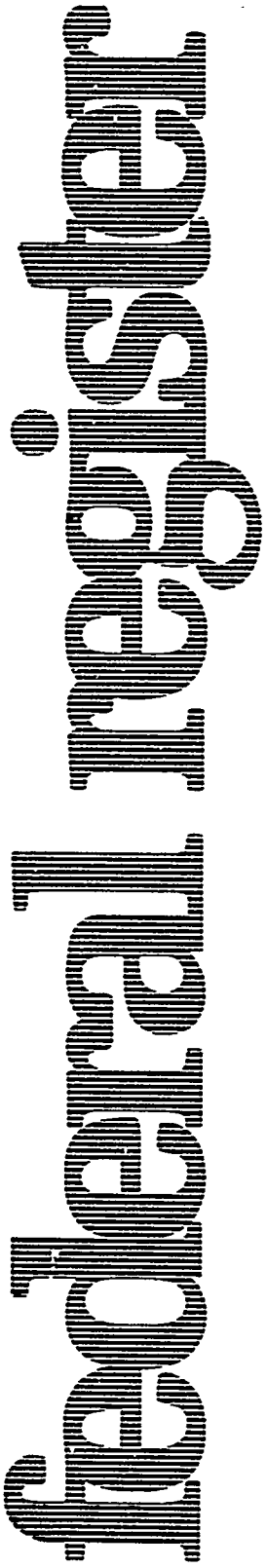
As this handbook went to press, the FDA had proposed to amend its current informed consent regulations to permit harmonization of Federal policies on emergency research, and to reduce confusion as to when such research can proceed without obtaining informed consent. The regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject prior to initiation of an experimental treatment. The exception would apply to a limited class of research activities involving human subjects who, because of their life-threatening medical condition and the unavailability of legally authorized

persons to represent them, are in need of emergency medical intervention and cannot provide legally effective informed consent. FDA is proposing this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized. Written comments to the proposed rule were due November 6, 1995. As this handbook went to press, the final rule had not been promulgated. *The proposed rule which appeared in the September 21, 1995, Federal Register can be found in the Appendix of this handbook.*

FDA regulates but does not, for the most part, support or conduct research. Its regulatory mandate, therefore, differs substantially from other DHHS agencies and other departments and agencies that conduct and support a significant amount of research. While the structural and functional requirements for IRBs in the FDA regulations are identical to DOE and DHHS regulations, the substantive provisions differ in several significant respects. IRBs should note that *where a protocol is subject to review under both FDA and DOE or DHHS human subjects regulations, both sets of regulations apply, and the requirements of both sets of regulations must be met.* This situation may arise, for example, with Treatment Investigational New Drug Exemptions or when applying the provisions on waiver of documentation of informed consent, in cases where both the FDA and DOE or DHHS have jurisdiction over the research.

B. 10 CFR Part 745, *Federal Policy for the Protection of Human Subjects; Notices and Rules*

(Document follows.)



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 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 included 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]
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§ ____.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.

(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

[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.

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 is § ____.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 releese 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 paragarph (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.
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).

[1] See Footnote 1 on page 28023.

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).

[1] See 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).

[1] See Footnote 1 on page 28023.

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).

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).

[1] See Footnote 1 on page 28023.

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.

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).

[1] See 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]

[1]Due 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.
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(h), 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 45879), 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 catgory 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 instituton'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, ') 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, 1988 (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 reducng 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 an 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. 289*l*-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.

C. DOE Order 1300.3, *Policy on the Protection of Human Subjects*

U.S. Department of Energy
Washington, D.C.

ORDER

DOE 1300.3

8-23-90

SUBJECT: POLICY ON THE PROTECTION OF HUMAN SUBJECTS

1. PURPOSE. To establish the Department's responsibilities for implementing policy set forth in 10 CFR Part 745, Protection of Human Subjects.

2. SCOPE. The provisions of this Order apply to all Departmental Elements and all contractors and subcontractors performing work for the Department, as provided by law and/or contract, and as implemented by the appropriate contracting officer. This includes non-DOE funded work at DOE-owned, -leased, or -controlled facilities.

3. REFERENCES.

   a. DOE 4300.2A, NON-DEPARTMENT OF ENERGY FUNDED WORK, of 12-19-86, which establishes the policy, responsibilities, and procedures for authorizing and administering non-DOE funded work performed under DOE contracts.

   b. Title 10 CFR Part 600, DOE Financial Assistance Regulations, which provides the policies and procedures for administration and management of all DOE financial assistance activities.

   c. Title 10 CFR Part 605, Office of Energy Research Special Research Grants Program Regulations, which provides the policies and procedures for the administration and management of basic and applied research grants awarded by the Office of Energy Research.

   d. Title 10 CFR Part 745, Protection of Human Subjects, which sets out DOE's regulations for protection of human subjects involved in research activities.

   e. Chapter 9 of Title 48 of the Code of Federal Regulations, Department of Energy Acquisition Regulations (DEAR), which provides the contracting policies established for DOE.

4. BACKGROUND. In December 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended and proposed a uniform set of regulations, based on those of the Department of Health and Human Services, to be adopted by all Federal agencies and departments conducting human subject research. A proposed model Federal policy for the protection of human subjects was published in the Federal Register on November 10, 1988, establishing this uniform set of regulations as a Common Rule. This Order implements 10 CFR Part 745, as currently written, and at such time that it is amended to conform with the Common Rule.

DISTRIBUTION:
All Departmental Elements

INITIATED BY:
Office of Energy Research

Continued—

DOE Order 1300.3 *(continued)*

DOE 1300.3
8-23-90

5. DEFINITIONS.

a. Assurance (Multiple Projects, (or) Single Project) means the written documentation, satisfactory to the Secretary of Energy, required from the prospective performing institution that assures institutional compliance with and implementation of DOE regulations for the protection of human research subjects.

b. Certification is the official notification by the institution to DOE in accordance with the requirements of 10 CFR Part 745, that a research project or activity involving human subjects has been reviewed and approved by an Institutional Review Board in accordance with an approved assurance (see paragraph 5a).

c. Contracting Officer is a person authorized to enter into, administer, or terminate contracts, financial assistance awards, and sales contracts and to make related determinations and findings.

d. DOE Contractors are entities who receive awards from DOE, including management and operating contractors (M&O), which manage, operate, or provide site services to DOE research or production facilities that are principally engaged in work for the Department.

e. DOE Facilities are any of the DOE-owned, -leased, or -controlled facilities.

f. Field Organization is a general term for any officially established Departmental component (excludes individual duty stations) located outside the Washington, D.C., metropolitan area.

g. Human Subject is 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.

h. Informed Consent is the legally effective consent by the human research subject, or the subject's legally authorized representative, to participate in research covered under this policy. It is obtained after providing to the subject the basic elements of informed consent as set forth in 10 CFR Part 745. Informed consent documents shall include disclosure of all potential risks and related consequences or adverse effects, as well as any benefits that may occur as a result of such participation.

Continued—

DOE Order 1300.3 *(continued)*

i. Institution is any public or private entity or agency (including Federal, state, and other agencies).

j. Institutional Review Board (IRB) is a board or committee charged with the responsibility for review of research activities involving human subjects conducted at, or sponsored by, the institution and approved by the Department of Health and Human Services (HHS) or the DOE. The composition of the IRB and details of its procedures and responsibilities are specified in 10 CFR Part 745 and included in the multiple, single, or other project assurance.

k. IRB Approval is the determination of the IRB that the research has been reviewed and may be conducted at an institution or facility within the constraints set forth by the IRB and by other institutional and Federal requirements.

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.

m. Management and Operating Contractors are those contractors designated by the Secretary in accordance with DOE policies.

n. Non-DOE Entities include other Federal agencies, State, regional, and local governments; educational institutions; private individuals, commercial firms, non-profit or not-for-profit organizations; international bodies; and foreign governments, individuals, firms, or organizations.

o. Non-DOE Funded Work is any work performed for non-DOE entities that utilize DOE facilities or contractor personnel and which is not funded, wholly or in part, by DOE.

p. Program Secretarial Officer (PSO) is a Secretarial Officer of the Department who has responsibility for research and development missions and Departmental programs.

q. Research is 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 Order, whether or not they are conducted under a program which is considered research for other purposes. For example some "demonstration" and "service" programs may include research activities.

6. POLICY. It is the policy of the Department of Energy that:

a. The rights and welfare of human subjects involved in research supported or sanctioned by DOE be protected in accordance with 10 CFR 745.

b. Until the requirements of this Order and 10 CFR 745 have been met, no research activity involving human subjects shall be initiated.

Continued—

DOE Order 1300.3 *(continued)*

DOE 1300.3
9-23-90

7. RESPONSIBILITIES AND AUTHORITIES.

a. The Secretary establishes Department of Energy policy for the protection of human subjects consistent with 10 CFR 745.

b. Director of Energy Research (ER-1) is responsible for the implementation of 10 CFR 745 within the Department in accordance with policy established by the Secretary.

c. Associate Director for Health and Environmental Research (ER-70).

(1) Develops and implements procedures on the protection of human subjects.

(2) Prepares and updates guidance to be followed for obtaining approval for human subject research.

(3) Approves all human subject assurances, negotiations, and evaluation processes. ER-70 may delegate authority for the evaluation and negotiation processes to the Heads of Field Organizations.

(4) Reviews all research with human subjects for compliance with DOE regulations and Orders and applicable Federal regulations. In a timely fashion, approves, rejects, or requests additional information on proposed work and provides written determination of human subject compliance to the PSO or appropriate Head of Field Organization.

(5) Investigates allegations of noncompliance with 10 CFR 745 and this Order, and recommends to the PSO or Head of Field Organization appropriate action required.

(6) Serves as the official DOE representative on the Interagency Human Subjects Coordinating Committee.

d. Program Secretarial Officers or their Designees.

(1) Implement the procedures established by ER-70.

(2) Review all proposals and applications to identify research involving human subjects.

(3) In accordance with procedures developed by ER-70, request determination of compliance by ER-70.

(4) Supply ER-70's determination of compliance with 10 CFR 745 to the cognizant contracting officer.

(5) Promptly notify ER-70 of known or potential adverse human health effects and issues of non-compliance in 10 CFR Part 745.

Continued—

DOE Order 1300.3 *(continued)*

e. Heads of Field Organizations or Their Designees.

(1) Fulfill responsibilities of PSOs under paragraph 7d for non-DOE funded work at DOE-owned or -leased facilities.

(2) Fulfill responsibilities of PSOs under paragraph 7d for DOE-funded work originating in the field office or Government-owned, Government-operated facilities.

f. Contracting Officers.

(1) Include in appropriate solicitations a provision requiring human subject research information in accordance with 10 CFR 745.

(2) Require receipt of complete assurance, certification, and ER-70 human subject approval documents, prior to initiation of research involving human subjects.

BY ORDER OF THE SECRETARY OF ENERGY:

JIM E. TARRO
Director of Administration and
Human Resource Management

D. DOE Order 4300.2C, *Work for Others (Non-Department of Energy Funded Work)*

U.S. Department of Energy
Washington, D.C.

ORDER

DOE 4300.2C

12-28-94

SUBJECT: WORK FOR OTHERS (NON-DEPARTMENT OF ENERGY FUNDED WORK)

1. Objectives. Work for Others, which is the performance of work and/or the utilization of Department of Energy facilities that is not directly funded by Department of Energy appropriations, has the following objectives:

   a. Provide assistance to other Federal agencies and non-Federal entities in accomplishing goals that may otherwise be unattainable and avoid the possible duplication of effort at Federal facilities.

   b. Where private facilities are inadequate, provide access for non-Department of Energy entities to highly specialized or unique Department of Energy facilities, services, or technical expertise.

   c. Increase Research and Development interactions between Department of Energy's facilities and industry to transfer technology originating in Department of Energy facilities to industry for further development or commercialization.

   d. Maintain core competencies and enhance the science and technology base at Department of Energy facilities.

2. Cancellation. This order supersedes DOE 4300.2B, Non-Department of Energy Funded Work (Work for Others), of 7-16-91.

3. Applicability. The provisions of this Order apply to all Departmental Elements and contractors performing Work for Others as provided by law or contract and as implemented by the appropriate Department of Energy Contracting Officer or authorized designee. This Order does not apply to the following:

   a. Services, products, or materials regularly produced for sale at schedule rates under Departmental programs (e.g., routine irradiation services, radioisotopes, heavy water, and Naval Petroleum Reserve oil sales).

   b. Work performed by non-DOE contractor personnel at a Department of Energy approved user facility (e.g., the National Synchrotron Light Source).

   c. Department of Energy funded work/services performed by one Department of Energy facility contractor for another.

   d. Visits or assignments of foreign nationals to Department of Energy facilities.

DISTRIBUTION:
All Departmental Elements

INITIATED BY:
Office of Organization and Management

Continued—

DOE Order 4300.2C *(continued)*

DOE 4300.2C
12-28-94

e. Consulting services by individual employees not representing themselves as Department of Energy employees or Department of Energy facility contractor employees.

f. Power marketing and transmission related work for the Power Marketing Administrations.

g. Cooperative Research and Development Agreements (CRADAs) performed under the National Competitiveness Technology Transfer Act of 1989.

h. Work for the Navy/DOE Naval Nuclear Propulsion Program.

i. Intergovernmental Personnel Act (IPA) assignments.

j. Other categories of work authorized by the Assistant Secretary for Human Resources and Administration, on a case-by-case basis.

4. Authority. See Attachment I, "References," for laws and regulations which govern Work for Others.

5. Policy. It is Departmental policy that Department of Energy resources be made available to non-Department of Energy entities; however, requirements delineated in paragraph 6 and other Department of Energy Orders and applicable regulations must be satisfied prior to performance of work.

6. Requirements.

a. Department of Energy facilities and resources may be made available to non-Department of Energy entities. A determination of the following must be made and certified in writing by the responsible Department of Energy Contracting Officer or authorized Department of Energy designee for work to be performed in the field. For work to be performed in Headquarters, a determination of the following must be made and certified by a Headquarters Contracting Officer.

(1) Is consistent with or complementary to Department of Energy missions and the missions of the facility to which the work is to be assigned;

(2) Would not adversely impact execution of assigned programs of the facility;

(3) Would not place the facility in direct competition with the domestic private sector; and

(4) Would not create a detrimental future burden on Department of Energy resources.

Continued—

DOE Order 4300.2C *(continued)*

b. For all Federal agencies, other than the Nuclear Regulatory Commission, a written statement on or with the funding document is required stating that the requesting agency has determined that entering into an agreement with Department of Energy is in compliance with the requirements of the Economy Act of 1932, as amended (31 United States Code 1535) [or other applicable authorizations, e.g., Executive Order 12333]. Those authorizations must be cited. In addition, a written statement is required stating that:

(1) the requesting agency has determined that entering into an agreement with the Department of Energy is in compliance with the Federal Acquisition Regulation (FAR) 6.002, and

(2) to the best of their knowledge, the work requested will not place the Department of Energy and its contractor in direct competition with the domestic private sector.

Sample Statement from a Federal Agency:

"This agreement is entered into pursuant to the authority of the Economy Act of 1932, as amended (31 United States Code 1535), [or other statutory authority references] and adheres to Federal Acquisition Regulation (FAR) 6.002. To the best of our knowledge, the work requested will not place the Department of Energy and its contractor in direct competition with the domestic private sector."

c. The requirements of 6a and 6b (if applicable) must be met prior to acceptance of reimbursable agreements and are also required for any modificatcns that are "out of scope" with the existing agreement. For previously approved work, with schedule and/or cost changes but no change in scope, the determinations and certification process is not required.

d. Responses to Broad Agency Announcements (BAAs), issued by other Federal agencies, are permitted when:

(1) Work consists of research and development that is part of a national program or Department of Energy mission and utilizes the Department of Energy's unique capability.

(2) Department of Energy contractor informs the cognizant Operations Office when submitting a proposal for review that the proposed work is in response to a Broad Agency Announcement.

(3) Proposals are reviewed and approved by the Department of Energy in accordance with this Order.

(4) Federal sponsors provide a written statement prior to acceptance that the Broad Agency Announcement is the only means used to acquire the work described in the Broad Agency Announcement.

Continued—

DOE Order 4300.2C *(continued)*

DOE 4300.2C
12-28-94

e. Pricing of work will be in accordance with DOE 2110.1A, Pricing of Departmental Materials and Services, of 2-16-84.

f. For Work for Others construction at a Department of Energy site which exceeds the General Plan Projects (GPP) threshold, approval of the cognizant Secretarial Officer and the Chief Financial Officer (CR-1) is required prior to initiation of work. In addition, all construction projects shall adhere to the following:

(1) Construction projects will be performed as required by DOE 4700.1, Project Management System, of 3-6-87.

(2) Title for permanent construction will pass to the Department of Energy upon completion of construction.

g. Equipment acquired as part of a project will be accounted for and maintained in the same manner as Department of Energy property. Disposition of equipment will be as previously agreed to or as instructed by the sponsor.

h. If subcontracting is necessary, selection of the subcontractor and work to be subcontracted will be made by the Department of Energy contractor. Subcontracted work is to be in direct support of the Department of Energy contractor.

i. The Department of Energy or its facility contractors may not respond to Federal agency Requests for Proposals (RFPs).

j. Intelligence-related activities will be conducted in accordance with Executive Order 12333, United States laws, other Executive Orders, Presidential Directives, and Director of Central Intelligence Directives.

7. Responsibilities and Authorities.

a. Assistant Secretary for Human Resources and Administration (HR-1).

(1) Establishes Work for Others policies in coordination with the cognizant Secretarial Officers.

(2) Prepares Annual Summary Report of Work for Others performed by the Department of Energy.

(3) Conducts periodic reviews of the implementation of this Order by cognizant Secretarial Officers and Heads of Field Elements.

(4) Approves requests for excluding projects from this Order.

Continued—

DOE Order 4300.2C *(continued)*

b. Chief Financial Officer (CR-1).

(1) Develops and publishes Work for Others accounting and budgeting procedures.

(2) Develops, in coordination with Heads of Departmental Elements, accounting and financial policy and standards for Work for Others.

(3) Prepares Work for Others financial reports as requested or required.

(4) Develops and maintains adequate financial information on Work for Others.

(5) Coordinates with cognizant Secretarial Officers to ensure the availability of funds for Work for Others projects accepted and performed at Headquarters.

(6) Concurs on Work for Others construction projects that exceed the General Plant Projects threshold.

c. Deputy Assistant Secretary for Procurement and Assistance Management (HR-5).

(1) Develops and publishes standard bilateral sales contract terms and conditions for use by Department of Energy Operations Offices.

(2) Develops procedures for deviations from standard terms and conditions.

(3) For projects accepted by Headquarters elements, ensures that the Associate Director for Procurement Operations accepts the project (unless delegated as in Paragraph 7j(2)).

d. Deputy Assistant Secretary for International Energy Policy (PO-7) reviews and concurs on all Work for Others requests directly funded by a foreign sponsor to ensure consistency with international agreements and foreign policy objectives.

e. General Counsel/Field Counsel.

(1) Provides advice to Department of Energy elements on conflict of interest issues.

(2) Provides Department of Energy legal advice and representation on questions related to non-competition and other legal issues.

(3) Establishes policy on patent and technical data, advises on patent and technical data clauses of contracts, and approves waivers of patent rights.

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f. Associate Director, Office of Health and Environmental Research (ER-70).

(1) Oversees the established Department of Energy system to ensure all proposed Work for Others research involving human and/or animal subjects complies with the established regulations for protection of these subjects.

(2) Reviews and approves proposed Work for Others projects involving human subjects for which approval authority has not been previously delegated to the Facility Contractor (research institution) through the Department of Energy or the United States Department of Health and Human Services Multiple Project Assurance.

(3) Reviews proposed Work for Others projects involving human and/or animal subjects that are of a sensitive nature (e.g., international locations, non-traditional sponsors).

g. Director, Office of Energy Intelligence (NN-30).

(1) Reviews and approves proposed intelligence-related Work for Others projects.

(2) Coordinates program reviews of all intelligence-related Work for Others projects with the participation of appropriate Field Elements.

(3) Is the central point of contact for coordination with sponsors of intelligence-related Work for Others projects.

(4) Assures the cognizant Secretarial Officer is informed of any problems relating to field management of intelligence-related Work for Others.

h. Director, Office of Research and Development (NN-20) reviews all Work for Others nuclear nonproliferation detection technology projects.

i. Director, Office of Space and Defense Power Systems (NE-50) reviews Work for Others proposals involving space nuclear reactor, non-commercial power reactor, and radioisotope power source projects, excluding Nuclear Regulatory Commission, fusion, weapons-related activities, naval propulsion reactors, and experimental reactors to establish an appropriate Nuclear Energy management role.

j. Program Secretarial Officers.

(1) For work accepted at Headquarters but performed in the field, the requirements of 6a and 6b must be met by the cognizant Field Element. Once these requirements are met, the responsible program Secretarial Officer can accept the project. If the responsible program Secretarial Officer has not been delegated authority to accept reimbursable agreements, HR-5 will accept. Once accepted, copies of all information must be forwarded to the Field Element(s) performing the work to instruct contractors to begin work.

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(2) For work accepted and performed at Headquarters, the responsible program Secretarial Officer will satisfy the requirements of Paragraphs 6a and 6b and obtain concurrence from CR-1 prior to acceptance of the project. If the responsible program Secretarial Officer has not been delegated authority to accept reimbursable agreements, HR-5 will accept.

(3) Coordinate with CR-1 to certify that funds are available prior to acceptance of Work for Others projects performed at Headquarters.

k. Cognizant Secretarial Officers.

(1) Develop and recommend changes in Work for Others policies to the Assistant Secretary for Human Resources and Administration.

(2) Provide notification to other appropriate Secretarial Officers of significant/sensitive Work for Others projects pursuant to Paragraph 71(5).

(3) Obtain CR-1 concurrence prior to approval of facility construction actions that exceed the General Plant Projects threshold.

(4) For each Department of Energy facility under their cognizance:

(a) Approve annual Work for Others levels and requests for increases to those levels in conjunction with recommendations of the responsible Head of Field Elements.

(b) Annually review the Work for Others Program to ensure consistency with Work for Others policies and procedures.

l. Heads of Field Elements.

(1) Function as the Departmental managers for Work for Others conducted in Department of Energy facilities under their purview. In this capacity, they are accountable to the cognizant Secretarial Officer for this work.

(2) Develop and implement procedures for the review, acceptance, authorization, and monitoring of Work for Others that are consistent with Department of Energy policies and procedures and encourage parallel review and processing by the Department of Energy, the sponsor, and the Facility Contractor.

(3) Delegate to the cognizant Department of Energy contractor authority to sign and execute bilateral sales contracts between the Department of Energy contractor and a non-Department of Energy entity. Such authority may be delegated only when Department of Energy-approved standard terms and conditions are utilized and a written Department of Energy determination is provided regarding the adequacy of the

Continued—

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contractor's management and administrative systems to properly execute and administer such contracts. When such authority is delegated, provide for the periodic review of the Department of Energy contractor policies and procedures and their implementation. Notwithstanding this delegation, the responsible Department of Energy Contracting Officer must ensure that the requirements of Paragraph 6a are satisfied.

(4) For each facility under their purview:

(a) Recommend annual Work for Others levels for approval by the cognizant Secretarial Officer.

(b) Monitor Work for Others levels to ensure consistency with the cognizant Secretarial Officer-approved levels and request increases from the cognizant Secretarial Officer.

(5) Notify the cognizant Secretarial Officer (using management judgment) of any Work for Others projects that involve sensitive subjects.

(6) Assure Department of Energy and/or contractor review of proposed Work for Others projects involving human and/or animal subjects for compliance with the established regulations for protection of these subjects.

(7) Assure that Work for Others projects under their purview are protected in accordance with applicable Department of Energy security, safeguards, and classification policies including the Site Security Plan or a supplemental security plan specific to the Work for Others project.

(8) Assure Department of Energy and contractors review for compliance with Department of Energy environmental, safety, and health requirements including the National Environmental Protection Act.

(9) Assure that the appropriate Headquarters element is involved in the Work for Others review process as described below:

(a) Cognizant Secretarial Officer reviews and approves all Work for Others construction at a Department of Energy site funded by a non-Department of Energy entity that exceeds the General Plant Projects threshold.

(b) PO-7 reviews and concurs on all proposed Work for Others projects sponsored by a foreign entity.

(c) NE-50 reviews and approves an appropriate Nuclear Energy management role for all proposed Work for Others projects identified in 7i.

Continued—

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(d) NN-30 reviews and approves all proposed intelligence-related Work for Others projects as defined in attachment 2, paragraph 6.

(e) NN-20 is notified of all nuclear nonproliferation detection technology Work for Others projects.

(f) ER-70:

1 reviews and approves all proposed projects involving human research subjects at Department of Energy facilities where no delegation of approval authority has been given pursuant to 7f(2).

2 is notified of all proposed Work for Others projects involving human and/or animal subjects that are of a sensitive nature pursuant to 7f(3).

(10) Establish and implement close-out procedures for Work for Others projects.

(11) Establish performance goals and measures to assess field performance and effectiveness of local Work for Others processes and impacts of subsequent improvements and/or additional requirements.

(12) Assure a project summary listing of information on each active Work for Others project is maintained. As a minimum, the information should include:

(a) Field points of contact

(b) Total estimated costs

(c) Sponsoring agency

(d) Project title/description

(e) Establish start/completion dates

(f) Assigned laboratory/contractor

(13) Assure project file information documenting policy compliance is maintained by Department of Energy and/or the performing contractor.

(14) Submit an Annual Work for Others Report for facilities under their purview to the cognizant Secretarial Officer and the Assistant Secretary for Human Resources and Administration by December 10.

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(15) Request, in coordination with the responsible Cognizant Secretarial Offices, exclusions from the requirements of this Order from the Assistant Secretary for Human Resources and Administration.

BY ORDER OF THE SECRETARY OF ENERGY:

ARCHER L. DURHAM
Assistant Secretary for
Human Resources and Administration

Continued—

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REFERENCES

1. FAR 35.017, Federally Funded Research and Development Centers (FFRDCs), which establishes Government-wide policies for the establishment, use, review, and termination of Federally Funded Research Development Centers.

2. FAR 17.5, Interagency Acquisitions Under the Economy Act, which prescribes policies and procedures for a Federal agency to obtain supplies or services from another Federal agency.

3. Atomic Energy Act of 1954, as amended (42 United States Code 2011 et seq.), Sections 31, 32, and 33, which authorizes the conduct of research and development and certain training activities for non-Department of Energy entities, provided that private facilities or laboratories are inadequate for that purpose. It authorizes such charges as may be appropriate for the conduct of those activities.

4. Economy Act of 1932, as amended (31 United States Code 1535), which authorizes an agency to place orders for goods and services, subject to availability, with another Government agency when the head of the ordering agency determines that it is in the best interest of the Government.

5. Intergovernmental Cooperating Act of 1968 (Public Law 90-577), as amended, which authorizes Federal agencies to perform work for state and local governments. Such work will be performed in accordance with the requirements of Office of Management and Budget Circular A-97.

6. Energy Reorganization Act of 1974 (Public Law 93-438), Section 205, which requires Federal agencies to furnish to the Nuclear Regulatory Commission (NRC) on a reimbursable basis, such research services as the Nuclear Regulatory Commission deems necessary and requests for the performance of its function.

7. Department of Energy Organization Act (Public Law 95-91), as amended, Section 649(b), which authorizes Department of Energy to permit the use of public and private agencies, corporations, associations, or other organizations or by individuals of any real property, or any facility, structure, or other improvement thereon, under the custody of the Secretary.

8. The National Competitiveness Technology Transfer Act of 1989 (Public Law 1010, Sections 3131, 3132, 3133, and 3159), prescribes technology transfer as a mission of the Department of Energy and its facilities.

9. Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480), as amended, Section 11, which states as public policy that the Federal Government shall strive to transfer federally owned or originated technology to state and local governments and the private sector.

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DOE Order 4300.2C *(continued)*

10. Executive Order 12333, "United States Intelligence Activities," part 1.13, which establishes responsibilities for the Department of Energy to support the U.S. intelligence community by providing expert technical, analytical, and research capability to others within the intelligence community and by participating in formulating intelligence collection and collection analysis requirements where Department of Energy expertise can contribute.

11. DOE 2110.1A, PRICING OF DEPARTMENTAL MATERIALS AND SERVICES, of 7-14-88, which establishes policy for setting prices and charges for materials or services sold or provided by the Department of Energy, either directly or through facility contractors, to organizations and persons outside of the Department of Energy.

12. DOE 2200.5A, FINANCIAL ACCOUNTING, of 1-7-93, Chapter IX, "Reimbursable Work, Revenues, and Other Collections," which establishes Department of Energy-wide financial policy and procedural guidance for certain interagency reimbursable actions and reimbursable actions with non-Department of Energy entities.

13. "Department of Energy Procedures for Intelligence Activities," which provides supplemental guidance/requirements for the conduct of Intelligence Work for Others.

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DOE Order 4300.2C *(continued)*

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Attachment II
II-1

DEFINITIONS

1. Acceptance is the official act of signing a reimbursable agreement, e.g., bilateral sales contract or interagency agreement, by a Department of Energy contracting officer or Department of Energy official to whom such authority has been delegated that commits Department of Energy and/or its contractor to perform Work for Others. Authority to sign and execute bilateral sales contracts can be delegated to the Department of Energy contractor by the Head of a Field Element.

2. Approved Missions of a Facility are areas of technical focus approved by the Department of Energy that support the Department's missions.

3. Cognizant Secretarial Officer is the Department of Energy official, at the Assistant Secretary level, who is responsible for the assignment of work, the institutional overview of a facility, or both.

4. DOE Program Missions are basic statutory activities of the Department of Energy, such as nuclear weapons and materials, production and support, energy technology development, non-nuclear energy research and development, and basic research.

5. Facility Contractors are entities that operate and maintain Government-owned facilities under contract with and for the benefit of the Department of Energy.

6. Intelligence-Related Work for Others is the following:

   a. Work which is directly funded by intelligence appropriations or by an organization specifically identified in Executive Order 12333 as an intelligence organization.

   b. Work funded by either the National Foreign Intelligence Program or the Tactical Intelligence and Related Activities Program.

   c. Work for which the Cognizant Technical Department of Energy Headquarters Official is the Director, Office of Energy Intelligence (NN-30).

7. Non-Department of Energy Entities includes other Federal agencies; state, regional and local governments; private or commercial firms, not-for-profit organizations; international organizations; and foreign governments.

8. Responsible Department of Energy Contracting Officer is a Department of Energy official with responsibility for administering the contract for the operation of a Department of Energy research or production facility. This person is generally the Head of a Field Element.

9. Space Nuclear and Non-Commercial Power Reactor and Radioisotope Power Work for Others Projects include those Research and Development projects associated with nuclear energy that are space nuclear reactor, non-commercial power reactor, and radioisotope power source projects but exclude Nuclear Regulatory Commission, fusion, weapons-related activities, naval propulsion reactors, and experimental reactors.

Continued—

DOE Order 4300.2C *(continued)*

10. Sponsor is an entity that provides funding for the performance of Work for Others.

11. Work for Others (WFO) is the performance of work for non-Department of Energy entities by Department of Energy/contractor personnel and/or the utilization of Department of Energy facilities that is not directly funded by Department of Energy appropriations.

12. Bilateral Sales Contract is a binding agreement (contract) between the Department of Energy or a Department of Energy facility contractor and a non-Federal entity that commits the Department of Energy to perform Work for Others activities.

E. 45 CFR 46, Subparts B, C, and D [protected classes], Department of Health and Human Services, Protection of Human Subjects

(Document follows.)

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 heartbeat, 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) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

Nullified June 10, 1993 (Public Law 103-43)

§ 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.

F. 45 CFR 46, Research Activities Which May Be Reviewed Through Expedited Review Procedures

(Document follows.)

RESEARCH ACTIVITIES WHICH MAY BE REVIEWED THROUGH EXPEDITED REVIEW PROCEDURES

Research activities involving no more than minimal risk *and* in which the only involvement of human subjects will be in one or more of the following categories (carried out through standard methods) may be reviewed by the Institutional Review Board through the expedited review procedure authorized in § 46.110 of 45 CFR Part 46.

(1) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

(10) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

Source: 46 FR 8392; January 26, 1981.

Institutional Responsibilities and Administrative Matters

A. Introduction

The performing institution is responsible for protecting the rights and welfare of human subjects in research and for complying with all applicable Federal, state, and local laws. Each institution engaged in human subjects research supported by the U.S. Department of Energy (DOE) must provide written certification (assurance) that it will comply with the requirements set forth in 10 CFR 745. The assurance must, at a minimum, include—

Reference Material Included In This Chapter

- Sample Institutional Policy Delegating Authority to the IRB (Figure 3a).
- Sample Delegation of Authority to the Authorized Institutional Official (Figure 3b).

- A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects in research conducted at or sponsored by the institution.
- Designation and support of one or more institutional review boards (IRBs) established in accordance with the requirements of this policy and provision of meeting space and sufficient staff to support the IRB's review and recordkeeping duties. *(See Section B of this chapter for further guidance.)*
- A list of IRB members that meet the requirements specified in 10 CFR 745.
- Written procedures that the IRB will follow, as specified in 10 CFR 745.
- Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department secretary, as specified in 10 CFR 745.

NOTE: The assurance must be certified by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by 10 CFR 745.

Institution officials may conduct further review and approve or disapprove research that has been approved by the IRB. Those officials, however, may not approve the research if it has not been approved by an IRB. Institution officials must assure compliance with IRB decisions to suspend or terminate approval of research projects.

The performing institution must establish an Office of Research Administration (ORA) or human subjects point of contact for approval of human research projects. An ORA is required for institutions holding Multiple Project Assurances with the National Institutes of Health (NIH).

The president or chief executive officer (CEO) of the performing institution must provide a written delegation of authority to the IRB to approve, disapprove, or modify research proposals. *(See Figure 3a, sample delegation of authority to the IRB.)*

Each institution should establish some type of internal review/oversight process to evaluate procedures and processes associated with human subjects research. Chapter 13 of this handbook goes into more detail on DOE's performance review system and NIH and Food & Drug Administration audit systems. It also provides checklists that institutions may use for self-evaluations or internal reviews.

B. Establishing an Institutional Review Board[1]

Institutions that are supported by a department or agency to which the Federal Common Rule applies must establish an IRB[2] to review and approve all research involving human subjects. Under Federal policy, institutions may establish more than one IRB when necessary, depending upon the structure of the institution and the kinds of human subjects research conducted there. Alternatively, an institution may designate another institution's IRB to review research upon approval of the appropriate department or agency. For example, if the research is supported by DOE, such designations must have prior approval of the Office of Health and Environmental Research (OHER), and if supported by the U.S. Department of Health and Human Services (DHHS), they must be approved by the Office for Protection from Research Risks (OPRR) within NIH.

The Authorized Institutional Official

Within the institution, there must be a point of responsibility for oversight of research and IRB functions. This individual should have the legal authority to act and speak for the institution as well as ensure that the institution will effectively fulfill its research oversight function. The authority may be delegated. If the institution's president or laboratory director or equivalent does not function as the authorized institutional official, a person who serves as the authorized institutional official should be provided with a written authorization to assume these responsibilities. *(See Figure 3b.)* The institution's president or laboratory director or equivalent should appoint or delegate the appointment of the individual. The individual selected should be high enough in the organizational structure to speak for the institution. The individual's title may be authorized institutional official or ORA administrator. The person in this position may have the additional responsibility of selecting the chairperson of the IRB and approval of all research projects for submission to the IRB. In addition, the authorized institutional official must provide written authority to the IRB to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both Federal regulations and local institutional policy. Research that has been reviewed and approved by an IRB may be subject to review and disapproval by officials of the institution; however, those officials may not approve research if it has been disapproved by the IRB.

Membership

Federal Policy Requirements

Title 10 CFR 745 provides that an IRB 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 in expertise, experience, and diversity of background—including diversity in racial and cultural heritage and sensitivity to issues such as community attitudes—to promote respect for its advice and counseling in

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[1]OPRR *1993 Protecting Human Research Subjects Institutional Review Board Guidebook,* pp. 1–3 through 1–7.

[2]The IRB may also be known as the "Human Use Committee," "Human Research Review Committee," or "Human Studies Board."

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. No IRB may consist entirely of members of one profession.

IRBs that regularly review research involving vulnerable categories of subjects, such as children, prisoners, pregnant women, and handicapped or mentally disabled persons, must consider the inclusion of one or more individuals knowledgeable about and experienced in working with these subjects.

IRBs must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are nonscientific. They must also include at least one member who is not affiliated with the institution and who is not an immediate family member of a person affiliated with the institution.

IRB Member Requirements

- Composed of five members or more, qualified by experience, expertise, diversity.
- Nondiscriminatory by gender.
- Knowledgeable about institutional commitments.
- Knowledgeable about regulations/laws and standards of conduct and practices.
- Representative of vulnerable or special populations.
- Representative of the community.
- Including at least one member with primarily scientific concerns.
- Including at least one member with primarily nonscientific concerns.
- Including at least one member not affiliated with the institution in any manner.
- Not limited to members of one profession.

In the interest of avoiding discrimination, 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 on the basis of gender. 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. These individuals may not vote.

No IRB member may participate in the review of any project in which he or she has a conflicting interest except to provide information requested by the IRB.

A list of current IRB members must be submitted to the assuring agency and must also be kept with the IRB records. The list must identify members by name, earned degree, representative capacity, and indicators of experience such as board certification and licenses sufficient to describe each member's chief anticipated contribution to IRB deliberations. This list must also note any employment or other relationships between each member and the institution. Possible relationships include, for example, being a 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.

Institutions that have an assurance with DOE or DHHS must also report any change in IRB membership to the appropriate office—OHER for DOE assurances and OPRR for DHHS assurances.

IRB Membership Considerations

An IRB may have as many members as necessary to perform its duties effectively. Care should be taken, however, to ensure it does not become so large that its management becomes cumbersome.

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. These individuals, however, may* not *vote with the IRB.

The nonaffiliated member of the IRB should be drawn from the local community at large; ministers, teachers, attorneys, business persons, or homemakers are possible candidates. The person selected should be knowledgeable about the local community and be willing and able to discuss issues and research from that perspective. Consideration should be given to the type of community from which the institution will draw its research subjects. If the community is rural and agricultural, a farmer would be appropriate. If the community is predominantly African American, Hispanic, or another ethnic group, then it would be advisable to have a member of that particular group or of those groups from whom the research population may be recruited. The nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

An investigator can be a member of the IRB; however, one stipulation must be observed without exception. The investigator, as a member, must not participate in the review and approval process for any projects in which he or she has a present or potential conflict of interest. Where the investigator-member has a conflicting interest, that person should be present only to provide information requested by the IRB and should be absent from the meeting room during the discussion and voting phase of the review and approval process. IRB minutes should state that these requirements have been met.

One of the most important actions to be taken in establishing an IRB is selecting the individual who will function as chairperson. The IRB chairperson should be a highly respected individual drawn from within or outside the institution and be fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of this individual. The IRB must be perceived to be fair, impartial, and immune from pressure, whether by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources.

Security Clearances

Because of the different mission characteristics of DOE national laboratories, specialized facilities, and production sites, some IRBs will require access to classified national security

information or restricted data in the performance of their duties. Therefore, where appropriate, security clearances should be obtained for a sufficient number of IRB members, including at least one nonscientist, to permit complete consideration of any classified work involving human subjects that may reasonably come before it for review. *(For more detailed information, see Chapter 7 of this handbook.)*

Institutional Responsibilities

Before any human subjects work can be conducted, the institution must provide a written assurance to the cognizant agency assuring that an IRB was established in accordance with Federal policy and that the proposed research will be approved by the IRB and conducted under the policy as well.

Staff, Space, and Supplies

The parent institution must provide the IRB with sufficient staff, meeting space, and supplies to support review and recordkeeping duties. *[For specific requirements, see 10 CFR 745.103 (B2) in Chapter 2.]*

Communication

The institution's chief executive officer or authorized institutional official must ensure that open channels of communication are maintained at all levels. It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of research directly to the appropriate institutional officials. Procedures must be established to protect reprisals against individuals who report concern over the conduct of research involving human subjects. It is vital that the IRB members, department heads, and other officials with responsibility for oversight of research have open and ready access to the highest level of authority within the institution.

Figure 3a. Sample Institutional Policy Delegating Authority to the IRB

Protection of Human Research Subjects

Overview

Introduction

[Institution] has an institutional responsibility for safeguarding the rights and welfare of human subjects of research. This instruction establishes [institution's] policy for complying with Federal, state, and local laws applying to human research subjects.

Policy

It is [institution's] policy that the rights and welfare of human subjects involved in research supported or sanctioned by the Department of Energy (DOE) be protected in accordance with 10 CFR 745, and in accordance with the special policies for protection of vulnerable groups such as pregnant women as defined in 45 CFR 46.

[Institution] policy includes the dual concept of minimized risk and maximized benefit to human subjects and an informed consent process that allows the subject to freely choose to participate without any deceit, duress, or coercion.

[Institution] has established the institutional review board (IRB) and the president or the CEO has granted the IRB the authority to approve or disapprove, or suspend or terminate previous approval of human research for the purpose of protecting the rights and welfare of human subjects. No individual or committee at [institution] may approve a research project that has been disapproved by the IRB.

Note: No individual at [institution] may initiate any research involving human subjects until such research has been approved by the IRB.

Scope

The information contained in this instruction applies to research involving human subjects that—

- Is sponsored by [institution],
- Is conducted by or under the direction of any employee of [institution] in connection with the employee's assigned responsibilities,
- Is conducted by or under the direction of any employee of [institution] using any property or facility of [institution], or
- Involves the use of [institution's] nonpublic information to identify or contact human research subjects or prospective subjects.

Note: Individuals who volunteer to be research subjects may or may not be [institution] employees.

Figure 3b. Sample Delegation of Authority to the Authorized Institutional Official

Sandia National Laboratories
Albuquerque, New Mexico 87185-5800
Livermore, California 94551-0969

Date: November 11, 1993

To: Distribution

From: SNL President

Subject: Delegation of Approval for Sandia Human Studies Board (HSB) Assurance Documents

The Sandia Human Studies Board (HSB) is responsible for safeguarding the welfare and rights of human research subjects in accordance with all applicable Federal, state, and local rules and regulations. I have appointed 18 members to the Human Studies Board, representing Sandia's technical, medical, and administrative staff and the external community. Dr. Larry Clevenger serves as Chairperson of the HSB, and Linda Erickson, Org. 3331, is the HSB Administrator.

The HSB process, covered in SLP 4565, "Protection of Human Research Subjects," includes several levels of institutional responsibility, including a sector or equivalent level approval prior to HSB review. The Human Studies Board then reviews the risks and benefits of proposed research and provides an independent "ethical" review of the proposed research.

Upon completion of the HSB approval of each research proposal, Sandia must submit a formal Assurance of Compliance document to the DOE Office of Health and Environmental Research (ER-70). I am delegating signature authority for HSB Assurance documents to James A. Tegnelia, Executive Vice President and Deputy Director. His signature upon each Assurance document will certify that Sandia has complied with and will continue to comply with the applicable Federal regulation (10 CFR 745).

C. Violations of Regulations: Sanctions

What sanctions are available if a researcher violates the protocols for protecting human subjects?

DOE regulations provide that Federal funds may not be expended for research involving human subjects unless the requirements of the Federal Policy for the Protection of Human Subjects (the Common Rule) are satisfied (10 CFR 745.122). Under DOE regulations, IRBs are authorized 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 (10 CFR 745.113). Any suspension or termination of approval of research by an IRB must include a statement of the reasons for the IRB's actions and must be reported promptly to the Department. DOE regulations further provide that the Department may require that any agency support for a project be terminated or suspended when the Department finds an institution has materially failed to comply with the terms of the Federal policy [10 CFR 745.123(a)].

In addition to these sanctions, DOE regulations authorize the Department to be guided by certain considerations in decisions about supporting or approving applications or proposals for research that would be covered by the Federal policy, such as—

- Whether the applicant has been subject to a termination or suspension.

- Whether the applicant or the person or persons who would direct or have directed the scientific and technical aspects of an activity have 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) [10 CFR 745.123(b)].

If a violation of the Federal policy is sufficiently serious that an organization's or individual's "present responsibility" has been impeached—for example, a willful violation of the regulations for the protection of human subjects—debarment from receiving Federal financial and nonfinancial assistance would also have to be considered (10 CFR Part 1036).

Civil and criminal sanctions may also be appropriate for some violations of the Federal policy. For example, institutions engaged in human research are required to certify that their applications or proposals have been reviewed and approved by an IRB (10 CFR 745.103); a false certification could result in civil liability under the Program Fraud Civil Remedies Act of 1986, 31 USC 3801–3812, or the False Claims Act, 31 USC 3729–3733, and in criminal liability under 18 USC 1001 and/or 18 USC 286, 287, and 371. Finally, improper human research activities could also be actionable, both civilly and criminally, under state law.

D. Voicing Concerns Regarding Current Human Subjects Research

The Common Rule does not contain whistleblower protection per se. DOE, however, supports traditional channels of complaints (including anonymous complaints) and encourages Federal and contractor employees to freely (and non-anonymously) voice their concerns and opinions to their managers regarding how DOE missions are being carried out without fear of reprisals or retaliation. Although concerns may be expressed anonymously, it is the Secretary's goal to foster a climate of open communication among employees and their management in order that problems can be resolved at an early stage and the mutual addressing of concerns be the normal means of doing business across the DOE complex.

To carry out this policy, employees throughout the DOE complex are asked to bring to the attention of their supervisors concerns regarding research involving human subjects that is being conducted by, at, or in collaboration or cooperation with their institutions; that is sponsored by or associated with their programs; or for which they may otherwise have responsibility in any manner (such as, for example, field-management responsibilities).

Other available avenues for communications include—

- The process maintained by each research institution for the anonymous disclosure of unethical practices or expressions of concerns regarding research at the institution.

- The Concerns Resolution Management Program, a process that is being established as part of the Secretary's openness initiative to receive all types of concerns and assure that they are appropriately addressed. In the interim, information on procedures to be followed may be obtained from the Office of Contractor Employee Protection (FM-40), (202) 586-8289, or the Office of General Counsel, General Law Division (GC-80), (202) 586-8665. Guidance may also be sought from the Office of General Counsel, Civilian Nuclear Programs Division (GC-52), (202) 586-6975.

- The DOE Office of the Inspector General. Allegations of criminal violations must be received or referred to this office or another law-enforcement organization for disposition.

Are There Whistleblower Clauses in the Management and Operating (M&O) Contracts?

Effective December 22, 1993, DOE Acquisition Regulation (DEAR) clause 970.5204-61(f) provides that M&O contractor costs incurred in connection with the contractors' defense of suits brought by employees or ex-employees of the contractor under section 2 (Major Fraud Against the United States) of the Major Fraud Act of 1988, including the cost of all relief necessary to make such employees whole, where contractors are found liable or settle, are unallowable (*Federal Register*, 58FR61625, Nov. 22, 1993). This provision does not give rights or protection to whistleblowers, but discourages contractor litigation with them.

NOTE: Major Fraud Act provisions limiting the allowability of costs incurred by contractors (that is, limiting reimbursement of such costs to the contractor by DOE) are effective with respect to any M&O contract entered into after November 19, 1988, *whether or not the contract contains a specific reference to their applicability* [Major Fraud Act, section 8(e)].

Single and Multiple Project Assurances

Introduction

Institutions that use U.S. Department of Energy (DOE) funding, facilities, or personnel to conduct research involving human subjects must provide DOE with an *assurance* that they are complying with 10 CFR Part 745. Many DOE laboratories hold a Single Project Assurance (SPA). Some have qualified for a Multiple Project Assurance (MPA). *(See Figure 4e).* The key difference between MPAs and SPAs is whether DOE headquarters must approve new human subjects projects before human subjects become involved.

Reference Materials Included in This Chapter

- Sample Single/Multiple Project Assurance (Figure 4a).
- Sample Transmittal Letter Requesting Approval of a New Project (for SPAs) (Figure 4b).
- Sample DOE Approval Letter (for SPAs) (Figure 4c).
- Sample Transmittal Letter Documenting Continuing Review (for SPAs) (Figure 4d).
- List of Assurances Held by DOE Laboratories (Figure 4e).

Following approval of each new project by the institutional review board (IRB), SPA facilities must seek headquarters' approval. For each new project, SPA institutions must send complete documentation, both the assurance of compliance with 10 CFR Part 745 and the project information, to the cognizant field office for transmittal to headquarters. Headquarters must provide approval before human subjects become involved in the project.

By contrast, MPA institutions are independently responsible for approving new human subjects research projects. Once the IRB approves a project, it may begin. While cognizant DOE field offices and headquarters exercise general oversight, they rarely, if ever, participate in granting initial project approval. Under Federal regulation, however, DOE may waive any prior approvals and examine any DOE-supported project.

After the initial approval of new projects, IRBs at both types of institutions must (1) review and approve projects at least once a year, and (2) annually report all approved projects to headquarters. Any adverse events must also be reported immediately to the IRB, to DOE headquarters, and to all funding sources.

Both SPA and MPA institutions may conduct expedited reviews of certain human subjects research. Under 10 CFR 745.110, a single, experienced IRB member selected by the IRB chairperson may conduct reviews when (1) approved research requires only minor changes within the review period or (2) research under review presents only minimal risk and falls totally or partly into a category eligible for expedited review, as determined by the Secretary of the Department of Health and Human Services (DHHS). *(See Chapter 2, Research Activities Which May Be Reviewed Through Expedited Review Procedures.)* Minimal risk is defined as being no greater in probability or magnitude than risks encountered in daily life or during the performance of routine physical or psychological tests. Note that if the reviewer disapproves the research, the full IRB must confirm the reviewer's decision.

Once expedited review has been conducted and approval has been given, however, SPA institutions must obtain headquarters' approval before human subjects become involved in the new project.

By Federal regulation, DOE and all other Federal agencies must recognize MPAs granted by DHHS. Thus, DOE laboratories like Lawrence Livermore National Laboratory and Lawrence Berkeley Laboratories, with DHHS-approved MPAs, are authorized to approve human subjects research funded by DOE.[1] Other funding entities such as the U.S. Army and the Department of Defense still require a second-level review at the funding agency headquarters level. Contact the specific funding entity for guidance.

Common Requirements for SPA and MPA Institutions

For each approved project—whether new or continuing—all institutions must submit project information to headquarters for the DOE Human Subjects Research Projects Database. *(See Chapter 12 for further guidance.)* This requirement applies whether an institution uses an SPA or has obtained MPA status from either DOE or DHHS.

Further, all institutions must immediately report the following events to field offices and headquarters:

- Any injuries to human subjects, unanticipated problems that involve risks to human subjects or others, and serious or continuing noncompliance with the requirements or determinations of the IRB.
- Any suspension or termination of the IRB's approval of research.
- Any change in the IRB membership.

[1]Under 10 CFR 745.123(a), DOE may terminate or suspend research supported by it for material failure(s) to comply with the terms of Part 745 (the Common Rule). Further, under section 745.124, DOE can impose additional conditions on the conduct of research prior to or at the time of its approval, when the Department believes that such conditions are necessary for the protection of human subjects involved.

Vulnerable Populations Requirements

Federal regulations require that IRBs give special consideration to protecting the welfare of vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. *(See 10 CFR 745.111 in Chapter 2.)* Research subject to DHHS regulations must comply with specific provisions on research involving fetuses, pregnant women, and human in vitro fertilization (45 CFR 46 Subpart B); prisoners (45 CFR 46 Subpart C); and children (45 CFR 46 Subpart D). Although DOE has not formally adopted these subparts, it is highly recommended that DOE institutions comply with the policies set forth in the subparts. Therefore, assurances from DOE institutions should include a statement of compliance with Subparts B, C, and D. DOE institutions holding National Institutes of Health (NIH) MPAs are already required to include this in their assurance. For example:

> [Institution] shall comply with the special policies of the regulations of the Department of Health and Human Services (DHHS) for research involving fetuses, pregnant women, human in vitro fertilization, prisoners and children, and shall consider additional safeguards in research involving individuals institutionalized as mentally disabled and other potentially vulnerable groups.

Requirements Checklist

Requirement	SPA Institutions	MPA Institutions (DOE or DHHS)
Must obtain DOE (ER-70) human subjects approval before new project begins.	yes	no
May conduct expedited review.	yes	yes
Must provide HQ with annual reports, including project data for the DOE Human Subjects Research Projects Database.	yes	yes
Must notify HQ immediately if human subjects experience adverse effects in any way.	yes	yes
Must notify HQ immediately if there is any evidence of noncompliance with the Federal regulation.	yes	yes
Must notify HQ if any research is conducted abroad or with foreign collaborators.	yes	yes

How To Qualify for MPA Status

To qualify for MPAs granted by DOE, institutions must demonstrate competence in protecting human subjects. Key factors are often the qualifications and experience of IRB members, evidence of their sensitivity and good judgment with respect to human subjects issues, and the production of orderly, complete, timely records and reports. *(See 10 CFR 745.107 in Chapter 2 or guidance in Chapter 3 for IRB composition requirements.)* DOE will award MPAs to institutions that have a satisfactory record of performance in the preparation, submission, and conduct of SPAs.

How To Apply for SPA or MPA Status

To apply for either an SPA or an MPA, institutions must use the sample format provided (Figure 4a), taking care to use the correct final page (A for an SPA, and B for an MPA). A roster of the current IRB membership must be attached. DOE will award the institution's first DOE MPA for a 3-year period. Subsequent renewals of the assurance will be granted for a 5-year period. Six months in advance of the expiration date, DOE will notify institutions that the MPA must be renewed.

Requests for MPA and SPA assurances must be submitted to—

Dr. Susan L. Rose
Health Effects and Life Sciences Research Division, ER-72
U.S. Department of Energy
19901 Germantown Road
Germantown, MD 20874-1290
Fax: (301) 903-8521
E-mail: human.subjects-info@oer.doe.gov

NOTE: Figures 4b, c, and d display examples of the correspondence between SPA institutions and DOE Headquarters regarding the approval of new and continuing projects.

Figure 4a. Sample Single/Multiple Project Assurance

[name of institution]

[Single/Multiple Project] Assurance to Department of Energy
Compliance With Regulations for the Protection of Human Subjects

[institution] hereby gives assurance that it will comply with the Department of Energy ("DOE") regulations for the Protection of Human Subjects (10 CFR Part 745, as amended, "DOE Regulations"), as specified below.

I. Statement of Applicability, Definitions, Ethical Principles, and General Policy.

A. Applicability. This Assurance covers all research involving human subjects (except as provided in paragraph I.B.) that:

1. Is sponsored or supported by [institution];
2. Is conducted by or under the direction of any employee of [institution] in connection with the employee's [institution]-assigned duties;
3. Is conducted by or under the direction of any employee of [institution] using any property or facility of [institution]; OR
4. Involves the use of nonpublic information of [institution] to identify or contact human research subjects or prospective subjects.

B. Exemption. This Assurance does not cover research in which human subjects are involved only through 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.

C. Definitions. For the purposes of this Assurance, the following terms have the meanings or applications stated:

1. *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this Assurance, whether or not they are conducted or supported under a program that is considered research for other purposes.
2. *Human subject* means a living individual about whom an investigator conducting research obtains:
   a. Data through intervention or interaction with the individual, or
   b. Identifiable private information.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

3. *Intervention* includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes.

4. *Interaction* includes communication or interpersonal contact between investigator and subject.

5. *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 that has been provided for specific purposes by an individual and that 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.

6. *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.

D. Ethical Principles.

1. [institution] is guided by report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report") [list any additional or alternative guidelines].

2. In addition, [institution] shall comply with the requirements of the DOE Regulations and any other pertinent Federal, state, or local laws or regulations that provide additional protections for human subjects.

E. Institutional Policy.

1. [institution] acknowledges and accepts full responsibility for protecting the rights and welfare of human subjects in all research covered by this Assurance, and for complying with all Federal, state, and local laws applicable to such research.

2. [institution] has established and shall maintain an Institutional Review Board ("IRB"), the [institution] Human Studies Review Committee ("Review Committee"), with the

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

responsibility to review all research covered by this Assurance and the authority to approve, disapprove, or suspend or terminate previous approval, of such research for the purpose of protecting the rights and welfare of human subjects.

3. [institution] shall provide meeting space for the IRB and sufficient staff to support the IRB's review and record-keeping duties.

4. [institution] shall encourage constructive communication among research administrators and investigators, clinical care staff, the members of the IRB, other institutional officials, and human subjects as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of the subjects.

5. Prior to the involvement of human subjects in any research covered by this Assurance:

   a. The research must be reviewed and approved by the IRB; and

   b. The informed consent of the subjects or their legally authorized representatives must be obtained in accordance with the IRB's requirements for the research, unless the IRB has specifically waived informed consent in accordance with the DOE Regulations and this Assurance.

6. [institution] shall submit certification of the IRB's approval of research in accordance with this Assurance to the supporting Federal department or agency, with the application or proposal for the research or by such later date as may be prescribed by the supporting department or agency.

7. [institution] shall exercise appropriate administrative overview, performed at least annually, to ensure that the [institution] policy for the protection of human research subjects is effectively implemented in compliance with the DOE Regulations and this Assurance.

8. [institution] shall comply with the special policies of the regulations of the Department of Health and Human Services for research involving fetuses, pregnant women, human in vitro fertilization, prisoners and children, and shall consider additional safeguards in research involving individuals institutionalized as mentally disabled and other potentially vulnerable groups.

9. [institution] shall comply with the requirements of the DOE Regulations and this Assurance related to cooperative research projects.

10. A copy of this Assurance and any future modifications (except changes in IRB membership) shall be provided to each individual who conducts or reviews research covered by this Assurance.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

II. Implementation.

A. Research Investigator. The responsibilities of the research investigator are as follows:

1. Determination of Human Subject Involvement.

   a. The research investigator shall determine whether research will involve human subjects, as defined in this Assurance.

   b. If the research investigator is uncertain whether research will involve human subjects, the investigator should request a determination from the IRB.

2. Preparation and Submission of Protocol.

   a. Prior to involving human subjects in research, the investigator shall prepare and submit to the IRB a protocol that includes:

      i. A complete description of the proposed research;

      ii. Provisions for the protection of human subjects in accordance with this Assurance, the DOE Regulations, and all other applicable laws and regulations; and

      iii. Sample(s) of proposed informed consent form(s).

   b. The research investigator shall submit the original research protocol and a supplement to the IRB when:

      i. It is proposed to involve human subjects in research that previously lacked definite plans for the involvement of human subjects. Applications for grants, cooperative agreements, or contracts that are submitted for funding or support with the knowledge that subjects may be involved within the period of support, but without definite plans for such involvement, need not be reviewed by the IRB before an award may be made. However, human subjects may not be involved in any project supported by such an award until the project has been reviewed and approved by the IRB in accordance with this Assurance and certification thereof has been submitted to the supporting department or agency. (Note: This provision is intended to cover activities such as institutional grants when selection of specific projects will be 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.)

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

ii. It is proposed to involve human subjects in research that previously had no plans for involvement of 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 the IRB, a certification submitted to the supporting department or agency, and final approval of the proposed change given by the supporting department or agency.

iii. It is proposed to change previously approved research during the period (of 1 year or less) for which approval is authorized. The research investigator shall not initiate any changes in previously approved research without the approval of the IRB, except when necessary to eliminate apparent immediate hazards to the subject(s).

c. The research investigator is responsible for submitting to the IRB a request for renewal of approval of ongoing research at least 1 month prior to the expiration date of the approval.

3. Compliance with Decision of IRB; Obtaining Informed Consent.

a. The research investigator shall comply with the IRB's decisions, conditions, and requirements regarding the research protocol.

b. The research investigator shall obtain and document informed consent prior to involving human subjects in the research, as required by the IRB, and shall retain signed informed consent forms at least 3 years after termination of the approval period.

4. Reporting. The research investigator shall promptly report to the IRB:

a. Any proposed changes in previously approved research.

b. Any injuries to human subjects, any unanticipated problems that involve risks to human subjects or others, or any serious or continuing noncompliance with the requirements or determinations of the IRB.

B. Institutional Review Board (IRB).

1. Duties and Authority. The IRB shall review and have authority to approve, require modifications in (as a condition of approval), or disapprove all research covered by this Assurance, or suspend or terminate previous approval of such research, to assure the protection of the rights and welfare of human subjects.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

2. Membership.

   a. The IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of the research covered by this Assurance. The IRB shall be sufficiently qualified through the experience, expertise and diversity in its 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.

   b. 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 [institution] commitments and policies, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas.

   c. The IRB shall not consist entirely of members of one profession, and nondiscriminatory efforts shall be made to ensure the IRB does not consist entirely of men or entirely of women.

   d. The 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.

   e. The IRB shall include at least one member who is not otherwise affiliated with [institution] and who is not a member of the immediate family of a person who is affiliated with [institution].

   f. No member may participate in the IRB's review of any project in which the member has a conflicting interest, except to provide information requested by the IRB, and the minutes of the IRB's meeting shall so reflect.

   g. The IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise in addition to that available on the IRB. These individuals may not vote with the IRB.

   h. The IRB members' names, earned degrees, representative capacities, relevant experience, and relationship (if any) with [institution] are set forth in Attachment "A" hereto.

3. Meetings. Except when an expedited review procedure is used, the IRB shall 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

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

areas. In order for research to be approved, it shall receive the approval of a majority of the members present at the meeting. The review committee shall meet not less than once per year, at the call of the chairperson, after appropriate notice to all members.

4. Continuing Review.

   a. The Review Committee shall establish and follow a schedule for review of all previously approved research at intervals appropriate to the degree of risk, but not less than once per year. When review intervals of less than 1 year are required, the IRB's notice of approval to the research investigator shall specify the review interval.

   b. The IRB shall observe or have a third party observe the consent process and the conduct of the research, if the IRB determines such observation should be required as a condition of approval.

   c. The IRB shall require verification from sources other than the investigators that no material changes have occurred since previous review by the IRB, if the IRB determines such verification should be required as a condition of approval.

5. Suspension and Termination of Approval. The 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.

6. Notice of Actions. The IRB shall notify investigators in writing and maintain records of its decisions to approve or disapprove proposed research, to require modifications as a condition of approval, or to suspend or terminate approval granted previously. If the IRB disapproves research, or suspends or terminates approval, it shall include in its written notification a statement of the reasons for its action and give the investigator an opportunity to respond in person or in writing.

7. Report to ____[institution]____ Officials and DOE. The IRB shall report promptly to the [director, president] of ____[institution]____, the [safety head], the Executive Secretary of the Environment, Safety and Health Council, DOE, and the supporting Federal department or agency (if other than DOE):

   a. Any injuries to human subjects, any unanticipated problems that involve risks to human subjects or others, or any serious or continuing noncompliance with the requirements or determinations of the IRB.

   b. Any suspension or termination of the IRB's approval of research.

   c. Any change in the membership of the IRB.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

C. Criteria for Approval of Research. In order to approve research covered by this Assurance, 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 do not unnecessarily expose subjects to risk, and, wherever 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 shall 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 shall 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, taking into account the purposes of the research and the setting in which the research will be conducted.

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, the DOE regulations and this Assurance.

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by, the DOE regulations and this Assurance.

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 research to protect the rights and welfare of those subjects.

D. Informed Consent. The IRB shall require that information given to subjects as part of informed consent is in accordance with the DOE regulations and this Assurance, or may waive obtaining informed consent in accordance with the DOE regulations and this Assurance, as set forth below.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

1. General Requirements for Informed Consent.

   a. An investigator shall not involve a human being as a subject in research covered by this Assurance unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative, or the IRB has specifically waived informed consent in accordance with the DOE Regulations and this Assurance.

   b. An investigator shall seek informed 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.

   c. The information given to the subject or the subject's representative shall be in language understandable to the subject or the representative.

   d. Informed consent, whether oral or written, may not include exculpatory language through which the subject or the subject's representative waives or appears to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, [institution], or its employees from liability for negligence.

2. Basic Elements of Informed Consent. Except as provided in paragraph 4 of this section, in seeking informed consent the following information shall be provided to each subject:

   a. 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.

   b. A description of any reasonably foreseeable risks or discomforts to the subject.

   c. A description of any benefits to the subject or to others that may reasonably be expected from the research.

   d. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

   e. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

f. For research involving more than minimal risk, an explanation as to whether any compensation is offered 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.

g. 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 subjects.

h. 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.

3. Additional Elements of Informed Consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

a. 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.

b. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Any additional costs to the subject that may result from participation in the research.

d. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

e. 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.

f. The approximate number of subjects involved in the study.

g. Any additional information that would meaningfully add to the protection of the rights and welfare of subjects.

4. Waiver of Informed Consent. The IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in this section, or may waive the requirement to obtain informed consent, provided the IRB finds and documents that:

a. The research involves no more than minimal risk to the subjects;

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;

c. The research could not practicably be carried out without the waiver or alteration; and

d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

5. Documentation of Informed Consent.

a. General Requirement for Documentation of Informed Consent. 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. Long and Short Forms. Except as provided in paragraph c of this section, the consent form may be either of the following:

i. A written consent document that embodies the elements of informed consent required by the DOE regulations and this Assurance. 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

ii. A "short form" written consent document stating that the elements of informed consent required by the DOE Regulations and this Assurance 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. Waiver of Documentation of Informed Consent. The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

i. 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

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

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

ii. 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.

6. Federal, State and Local Law. The informed consent requirements set forth above are preempted by any applicable Federal, state, or local laws that require additional information to be disclosed in order for informed consent to be legally effective.

7. Emergency Medical Care. The informed consent requirements set forth above are not 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.

E. Expedited Review.

1. The IRB may use an expedited review procedure to review:

a. Research found by the reviewer(s) to involve no more than minimal risk and in which the only involvement of human subjects will be in one or more of the following categories:

i. Collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

ii. Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

iii. Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

iv. Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more often than two times per week, from subjects 18 years of age or older who are in good health and not pregnant.

v. Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

vi. Voice recordings made for research purposes such as investigations of speech defects.

vii. Moderate exercise by healthy volunteers.

viii. The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

ix. Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

x. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

b. Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

2. Expedited review shall be carried out by the chairperson of the IRB or by one or more experienced reviewers designated by the chairperson from the members of the IRB.

3. In expedited review, the reviewer(s) may exercise all of the authorities of the IRB except that the reviewer(s) may not disapprove the research. A research activity may be disapproved only after review in accordance with the procedure for initial review set forth in section II.B.1.

4. Summaries of all research proposals approved by expedited review shall be distributed on a regular basis to all members of the IRB.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

F. Cooperative Research. In the conduct of cooperative research projects that are covered by this assurance and involve [institution] and one or more other institutions, [institution] and the other institution(s) shall each be responsible for safeguarding the rights and welfare of human subjects. With the approval of DOE, [institution] may enter into a joint review arrangement, rely upon the review of another institution's qualified IRB, or make similar arrangements to avoid duplication of effort.

G. Record-Keeping.

1. The IRB shall prepare and maintain adequate documentation of the IRB's activities, including the following:

   a. 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.

   b. 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. Copies of the minutes shall be provided to the [director, president] of [institution]; the Division Leader of the Health, Safety and Environment Division; and the Executive Secretary of the Health, Safety and Environment Council.

   c. Records of continuing review activities.

   d. Copies of all correspondence between the IRB and the investigators.

   e. A list of the IRB members' names, earned degrees, representative capacities, relevant experience, and relationship (if any) with [institution].

   f. This Assurance, any modifications thereto, and any procedures not described therein.

   g. Statements of significant new findings provided to subjects, as required by the DOE Regulations and this Assurance.

2. The records required by this assurance shall be retained for at least 3 years, and records relating to research that 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 DOE at reasonable times and in a reasonable manner.

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

A. To be used for a Single Project Assurance

III. Institutional Endorsement and DOE Approval.

With regard to the project entitled, _____,
Number _____, submitted on behalf of _____[institution]_____,
I certify that _____[institution]_____ has complied, and will continue to comply, with 10 CFR Part 745, as amended, as specified above.

Signature: _____ Date: _____

Name: _____

Title: _____

Address: _____

_____

Telephone: _____

I certify that the _____[institution]_____ IRB reviewed and approved the above project in accordance with 10 CFR Part 745, as amended, as specified above.

Signature: _____ Date: _____

Name: _____

Title: Chairman, _____ IRB

Address: _____

_____

Telephone: _____

All parts of the foregoing Assurance are in compliance with the requirements of 10 CFR Part 745.

DOE Approving Official:

Signature: _____ Date: _____

Name: _____

Title: _____

Address: _____

_____

Telephone: _____

Continued—

Figure 4a. Sample Single/Multiple Project Assurance *(continued)*

B. To be used for a Multiple Project Assurance

A. Authorized Institutional Official:

Signature: _____

Name: _____

Title: _____

Address: _____

_____

_____

Telephone: _____

B. DOE Approving Official:

Signature: _____

Name: _____

Title: _____

Address: _____

_____

_____

Telephone: _____

C. Effective Day of Assurance: _____

D. Expiration Date of Assurance: _____

Figure 4b. Sample Transmittal Letter Requesting Approval of a New Project (for SPAs)

Date

Note: DOE laboratories and/or dedicated facilities should address transmittal letters to the cognizant DOE field office. All other institutions should send transmittal letters directly to the address below.

To cognizant DOE field office
or
Protection of Human Subjects
Mail Station ER-70
Office of Health and Environmental Research
U.S. Department of Energy
Washington, D.C. 20585

Dear :

I request formal Department of Energy (DOE) approval of the following project(s) in which human volunteers will participate:

Title:
Principal Investigator:
Funding Source:
Identifying No.:

An "Assurance to Department of Energy of Compliance with Regulations for the Protection of Human Subjects" and the current membership of the Human Studies Review Committee (or IRB) are enclosed with Institutional Endorsement and DOE approval sheets for each of the new projects. The assurance document incorporates all features required by the Federal Common Rule governing protection of human subjects in research. The appendix contains the informed consent document, experimental protocol, proposal of work statement for each project, and a completed Data Summary form.

If you require additional information, please call me.

Sincerely,

Name and Title

Figure 4c. Sample DOE Approval Letter (for SPAs)

Date

Institution Name and Address

Dear :

We have received a submission of one single project assurance of human subjects research at *[institution]*. This submission has been reviewed and found to be complete and satisfactory and fully complies with the Office of Health and Environmental Research (OHER) human subjects approval requirements.

1. Title: "_____"
   Principal Investigator:
   Project Number:
   Funding Source:

It is understood that all further human subjects projects will be submitted according to the same procedures in the future, and that an annual Institutional Review Board approval form will be provided to us for the projects in the future.

Sincerely,

Susan L. Rose, Ph.D.
Human Subjects Program Manager, Health Effects
and Life Sciences Research Division
Office of Health and Environmental
Research, Office of Energy Research

Figure 4d. Sample Transmittal Letter Documenting Continuing Review (for SPAs)

Date

To cognizant DOE field office
or
Protection of Human Subjects
Mail Station ER-70
Office of Health and Environmental Research
U.S. Department of Energy
Washington, DC 20585

Dear :

Enclosed is the material documenting the results of the continuing review of a project(s) employing human volunteers, entitled ***[title here]***. The project was reviewed and approved by the ***[name of institution]*** Institutional Review Board at the ***[date]*** meeting.

The enclosed form(s) provide information on the status of this study.

Sincerely,

Name and Title

Figure 4e. List of Assurances Held by DOE Laboratories

The following list of DOE laboratories indicates the type of assurance (MPA or SPA) that each laboratory holds (as of August 1, 1995). *(For a list of all DHHS, NIH MPA institutions, refer to the Appendix, Chapter 15.)*

Institution	Type of Assurance
Argonne National Laboratory (ANL), Argonne, IL	DOE, SPA
Brookhaven National Laboratory Associated Universities, Inc. (BNL), Upton, NY	DHHS, MPA
Hanford Environmental Health Foundation (HEHF), Richland, WA	DOE, SPA
Inhalation Toxicology Research Institute (ITRI) (The Lovelace Institutes), Albuquerque, NM	DHHS, MPA
Idaho National Engineering Laboratory (INEL), Idaho Falls, ID	DOE, SPA
Lawrence Berkeley National Laboratory (LBNL), Berkeley, CA AND University of California, Berkeley (UCB), Berkeley, CA	DHHS, MPA (JOINT)
Lawrence Livermore National Laboratory (LLNL), Livermore, CA	DHHS, MPA
Los Alamos National Laboratory (LANL), Los Alamos, NM	DOE, MPA
Oak Ridge Institute for Science and Education (ORISE), Oak Ridge, TN AND Oak Ridge National Laboratory (ORNL), Oak Ridge, TN	DHHS, MPA (JOINT)
Pacific Northwest Laboratory (PNL), Richland, WA	DOE, MPA
Rocky Flats Laboratory, Golden, CO	DOE, SPA
Sandia National Laboratories (Sandia), Albuquerque, NM, and Livermore, CA	DOE, SPA
University of California, Los Angeles (UCLA), Los Angeles, CA	DHHS, MPA
University of California, San Francisco (UCSF), San Francisco, CA	DHHS, MPA

NOTE: This is not a complete list of DOE research institutions. Some DOE facilities do not conduct human subjects research and hence have no MPA or SPA.

IRB Responsibilities and Procedures

A. Introduction

Responsibilities

- The institutional review board (IRB) reviews all proposed and continuing research involving human subjects, data, or specimens to determine acceptability in terms of applicable Federal laws and regulations, the institution's commitments and policies, applicable law, and standards of professional conduct and practice.

No individual or committee at the institution may initiate any research involving human subjects that has not been approved by the IRB.

- The IRB has the authority to approve, to grant conditional approval, or to disapprove proposed research and to conduct continuing review of previously approved research projects. The IRB should observe and verify any changes in the research and may suspend or terminate approval of research that is not being conducted in accordance with the IRB's decisions, conditions, and requirements or that has been associated with unexpected serious harm to subjects.

- No individual or committee at the institution may initiate any research involving human subjects that has not been approved by the IRB.

- The IRB has a written delegation of authority from its institution, granting the IRB all powers necessary to fulfill responsibilities, as set forth in 10 CFR 745. A copy of this delegation of authority has been sent to the U.S. Department of Energy (DOE). (*See Chapter 3 for a sample Delegation of Authority.*)

Stages of IRB Review

- Initial Review.
- Continuation Review.
- Modification Review.
- Adverse Reaction/Event Review.

- The IRB reviews all reported adverse events associated with human subjects research conducted at the institution.

Membership

As stated in 10 CFR 745, IRB membership must—

- Include at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
- Be sufficiently qualified through the experience, expertise, and diversity of its members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes.
- 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.
- Include one or more individuals who are knowledgeable about and experienced in working with any vulnerable subjects (such as children, prisoners, pregnant women, the mentally disabled) that may be participating in research to be reviewed.
- Include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- 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.

As stated in 10 CFR 745, IRB membership may not—

- Consist entirely of members of one profession.
- Have a member 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.

NOTE: 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. These individuals, however, may *not* vote with the IRB.

As stated in 10 CFR 745—

- Every nondiscriminatory effort should be made to ensure that no IRB consists entirely of men or entirely of women.

Procedures

As stated in 10 CFR 745—

- Except when an expedited review procedure is used, an IRB must 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 research to be approved, it must receive the approval of a majority of those members present at the review.

- An IRB must notify investigators in writing of its decisions to approve or disapprove proposed research, to require modifications as a condition of approval, or to suspend or terminate previous approval. Any notification of disapproval, suspension, or termination must state reasons for the action so that the investigator may respond in person or in writing.

- The IRB letter of approval must specify the review interval (depending on the degree of risk, but at least once a year).

- An IRB must prepare and maintain adequate documentation of IRB activities. Such documentation must include—

  - Copies of all research reviewed including, for example, scientific evaluations, if any, and the approved and dated consent document.

  - Meeting minutes.

  - Records of continuing review activities.

  - Copies of all correspondence between the IRB and investigators.

  - A list of IRB members.

  - Written procedures for the IRB.

  - Statements of significant new findings provided to subjects.

NOTE: Records must be retained for at least 3 years after completion of research. All records must be accessible for inspection and copying by authorized representatives of the funding Department at reasonable times and in a reasonable manner.

B. Types of IRB Review

Full Board Review

Full board review is required when research does not meet the requirements for expedited review or for exemption from human subjects requirements. Requirements for conducting a full board review include the following—

Reference Materials Included In This Section

- OPRR Reports, 95–02 (Figure 5a).
- OPRR Reports, 95–01 (Figure 5b).

- Review must be conducted at a convened meeting.
- A majority of the members of the IRB must be present at the meeting.
- At least one member whose primary concerns are in nonscientific areas must be present at the meeting. [In addition, Food and Drug Administration (FDA) policy requires that a physician be present.]
- To approve research, the IRB must determine that all of the requirements specified in 10 CFR 745.111 are satisfied.
- For research to be approved, it must receive approval of a majority of the members present at the meeting.
- IRB members who have a conflicting interest in a research project cannot participate in the review except to provide information.
- The IRB must notify investigators and the institution in writing of its decision to approve, modify, or disapprove the research.

Main Function of IRB Review: To Assure That—

- Risks are minimized; reasonable in relation to anticipated benefits.
- There is informed consent.
- Rights and welfare of subjects are maintained.

Expedited Review

Expedited review is a review of proposed research by the IRB chairperson or a designated voting member or group of voting members rather than by the entire IRB. Expedited review may be conducted when the research is found to involve no more than minimal risk and it falls totally or partly into a category eligible for expedited review, as determined by the Secretary of the Department of Health and Human Services (DHHS). *(See Chapter 2, 10 CFR 745.110 and Research Activities Which May Be Reviewed Through Expedited Review Procedures.)* Expedited procedures can also be used to review minor changes in previously approved research.

Following are additional requirements for expedited review:

- The reviewer may exercise all of the authorities of the IRB, with the exception that the reviewer may *not* disapprove research.
- In conducting the review, a determination must be made that the research does meet the conditions required for use of expedited procedures.
- To approve the research, the reviewer must make the determination that all of the requirements specified in 10 CFR 745.111 are satisfied.
- The IRB must adopt a method for keeping all members advised of research proposals that have been approved using expedited procedures.

Research qualifying for expedited review includes—

- Collection of hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.
- Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
- Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes procedures such as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (e.g., x-rays, microwaves).
- Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more often than 2 times per week, from subjects 18 years of age or older who are in good health and not pregnant.
- Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
- Voice recordings made for research purposes such as investigations of speech defects.
- Moderate exercise by healthy volunteers.
- The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

- Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

- Research on drugs or devices for which an Investigational New Drug Exemption or an Investigational Device Exemption is not required.

For further guidance on expedited review process and research that qualifies for expedited review, refer to the OPRR Reports 95–02 (Figure 5a) in this chapter and to 10 CFR 745.110 and 45 CFR 46, Research Activities Which May Be Reviewed Through Expedited Review Procedures, found in Chapter 2 of this handbook.

Exempt Research Projects

A research project is exempt when IRB review of proposed research indicates that research does not involve human subjects as defined in 10 CFR 745 and/or the only involvement of human subjects is in one of the categories listed under 10 CFR 745.101(b)(1)-(6). Human subjects regulations do not apply to exempt projects. It is the responsibility of the assuring institution to determine the exempt status of research projects involving human subjects. Any research project involving human subjects that is thought to be exempt must be submitted to the IRB for determination. IRB determination of exempt status should be documented in writing to the principal investigator (PI) and maintained in the institutional project research records.

Any research project involving human subjects that is thought to be exempt must be submitted to the IRB for determination.

Exemption Categories

Research activities are exempt from the Federal Policy for the Protection of Human Subjects when the *only* involvement of human subjects falls within one or more of the categories below.

1. Research conducted in established or commonly accepted educational settings involving normal educational practices.

2. Research involving the use of educational tests, 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*

Exemptions Do Not Apply to Research Involving—

- Pregnant women.
- Fetuses.
- Prisoners.

Survey/Interview Exemption Does Not Apply to—

- Research involving children.

Observation of Public Behavior Exemption Does Not Apply to—

- Research involving children, except when investigator does not participate in activities being observed.

- 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 not exempt under "2" above may be exempt if, in the use of educational tests—

   - The human subjects involved 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.

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 which 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.

   - 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 if—

   - Wholesome food without additives are consumed, or

   - 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.

NOTE: In special cases, an institution may consider a project exempt if there is a signed institutional assurance by a cooperating institution's qualified IRB. This eliminates duplication of reviews. *(See Chapter 8, Cooperative Research Efforts.)*

For further guidance on exempt research projects, refer to the OPRR Reports 95–02 (Figure 5a) in this chapter.

Continuing Reviews and Project Oversight Considerations

Continuing Periodic Review

According to the Common Rule: "An IRB shall conduct continuing review of research . . . at intervals appropriate to the degree of risk, but not less than once per year . . . ." Review must be meaningful and substantive. An expedited review process may be used only if the original proposals as well as the proposed continuation are eligible for expedited review under the Common Rule. The IRB review should consider the protocol and any changes, the consent form(s), and an annual report. The annual report should include, at a minimum—

Requirements for Conducting Continuation Review

- Continuing review of research must be conducted at intervals appropriate to the degree of risk, but not less than once per year (i.e., IRB cannot approve a research project for more than 12 months).
- When conducting a continuation review, full review procedures should be used unless the research meets the expedited review criteria.

- The number of subjects accrued in the last year and the number proposed for the coming year.
- A description of any adverse events, unanticipated risks, or complaints about the research and the corrective actions taken.

In some cases, the consent form may require modification to include new risk considerations. After review and approval, the consent form must indicate the date of review or expiration. A copy of the dated approved consent form must be sent to the investigator for use during the year. *(For further guidance on continuing reviews, refer to OPRR Reports 95–01, Figure 5b.)*

Unanticipated risks and adverse events should be reported on an ongoing basis according to the procedures laid out in Chapter 10. They should also be summarized in the annual report along with any corrective actions taken. IRBs should use such reports as indicators of when additional oversight of a project may be merited.

Frequency of continuing reviews may, of course, exceed the minimum standards. The IRB can set special review standards in order to provide better oversight of individual projects. For example, reviews can be set at intervals (for example, every 3, 6, or 9 months) appropriate to the degree of risk (high, medium, or low) as determined by the IRB. This model is common in hospitals conducting drug trials. The committee could also require a continuing review after an initial subset of subjects are studied. Another possibility is to use the continuing review report to gather specific information on points of concern raised during the initial review (e.g., Did the subjects respond as expected? At what point in the study did subjects drop out and what reason did they give for not wanting to continue?).

Additional Oversight Committees

The IRB may appoint a committee with special expertise to provide additional oversight over certain research projects at their institution. Additional oversight mechanisms may be provided, for example, by Radioactive Drug Research Committees (RDRCs) and Data Safety Monitoring Boards (DSMBs). RDRCs are required and authorized by FDA to review the use of certain

experimental radioactive compounds in human subjects. The IRB should require that the RDRC report any questionable studies to the IRB; at most institutions, only the IRB has the authority to act on RDRC findings.

DSMBs review actual data generated by a specific study on a regular basis. They may be required by the funding agency, FDA, or the IRB. Most DSMBs are appointed in response to problems with a study or out of concern over the initiation of a particularly complex project such as a high-risk clinical trial or a multicenter study. Problems or questions are referred to the IRB for action, although simultaneous reports to the investigator(s), the funding agency, and/or FDA may be required.

Figure 5a. OPRR Reports, 95–02

Number 95–02
Human Subject Protections

OPRR Reports

NIH PHS HHS

May 5, 1995

Subject: Exempt Research and Research That May Undergo Expedited Review

Dear Colleague:

The purpose of this letter is to assist Institutional Officials and Institutional Review Board (IRB) Chairs in interpreting the term "exempt" research and identifying research for which "expedited review" is appropriate.

Research activities involving human subjects that are **exempt** from IRB review are identified in 45 CFR 46.101(b)(1)-(6). (Institutions and IRBs may not create new categories of exempt research under 45 CFR Part 46.) Institutions should have a clear policy in place on who shall determine what research is exempt under §46.101(b). Those persons who have authority to make a determination of what research is exempt are expected to be well-acquainted with interpretation of the regulations and the exemptions. In addition, the institution should be prepared to reinforce and review, as necessary, the method of determining what is exempt. OPRR advises that investigators should not have the authority to make an independent determination that research involving human subjects is exempt and should be cautioned to check with the IRB or other designated authorities concerning the status of proposed research or changes in ongoing research.

Institutions may elect to review all research under the auspices of the institution even if the research qualifies for exemption under §46.101(b). An institution with a Multiple Project Assurance (MPA) or Cooperative Project Assurance (CPA) should indicate in its Assurance if and how exempt research is reviewed. It is incumbent on the institution to advise investigators and others involved in the conduct and administration of research involving human subjects of the institutional policies for reviewing exempt research.

Expedited review procedures are described in §46.110. In short, the IRB Chair or one or more experienced reviewers, designated by the Chair from among members of the IRB, review the research and approve it or refer it to the IRB for full IRB discussion. Attached is the list of activities that may be reviewed through expedited review procedures (Federal Register 46: 8392, Jan. 26, 1981).* (Additions to, and extrapolation from, this list by the institution or the IRB are not appropriate.) To qualify for expedited review, an activity must: (1) involve no more than minimal risk **AND** be found on this list, **OR** (2) be a minor change in previously approved research during the period of 1 year or less for which approval is authorized by the IRB. It is OPRR policy that only institutions with MPAs or CPAs may use expedited review as in the condition of (1), above, if appropriate.

Continued—

*Attachment not included.

Figure 5a. OPRR Reports, 95–02 *(continued)*

Consultants may assist the IRB Chair in making decisions in expedited review, but expedited review cannot be performed solely by persons who are not members of the IRB. In conducting expedited review, the IRB reviewers may exercise all of the authorities of the IRB except that they may not disapprove the research. A research activity may be disapproved only after review in accordance with the ordinary, nonexpedited procedure set forth in § 46.108(b). The IRB shall adopt a method for keeping all IRB members advised of research proposals that have been approved under the expedited review procedure. The institution's Assurance should specify how expedited review will be carried out.

Institutions and IRBs are reminded that expedited review is not ordinarily appropriate at the time of continuing review when the research qualifies for full board review (see OPRR Reports 95–01).

The concept of **exempt** research and the practice of **expedited review** of research can come together, as some institutions choose to provide an additional measure of protection for human subjects by reviewing what would be exempt research under § 46.101(b) in an expedited manner. This is acceptable, since expedited review of that which is exempt exceeds the minimum requirements for both in 45 CFR Part 46.

The categorization of human subjects research as "exempt" from IRB review or appropriate for "expedited" IRB review is intended to streamline IRB procedures with no diminution of protection for human subjects. Please employ these concepts in that spirit. OPRR's Health Research Policy Officer, Dr. Joan P. Porter, is available at 301-496-7005 (ext. 206) for any questions you may have.

Sincerely,

Gary B. Ellis, Ph.D.
Director
Office for Protection from Research Risks

Attachment*

*Attachment not included.

Figure 5b. OPRR Reports, 95–01

Number 95–01
Human Subject Protections

OPRR Reports

NIH PHS HHS

January 10, 1995

Subject: Continuing Review—Institutional and Institutional Review Board Responsibilities

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) Chairs throughout the country as a reminder of IRB and institutional responsibilities in continuing review of research activities.

The Department of Health and Human Services (HHS) Regulations, Title 45 Code of Federal Regulations Part 46 (45 CFR 46), require at Section 46.109(c) that "an IRB shall conduct continuing review covered by this policy at intervals appropriate to the degree of risk, but not less than once per year . . . ."

Continuing review must be substantive and meaningful. Review by the convened IRB, with recorded vote, is required unless the research is otherwise appropriate for expedited review under Section 46.110. Ordinarily, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review. It is also possible that research activities that were previously judged as exempt in accordance with Section 46.101(b), or were qualified for expedited review in accordance with Section 46.110, have changed or will change, such that other than expedited IRB review is now required.

OPRR interprets "not less than once per year" review to mean review on or before the 1-year anniversary date of the previous IRB review required by 45 CFR 46, even though the research activity may not begin until some time after the IRB has given approval.

The regulations at 45 CFR 46 outline the minimum requirements for continuing review. They do not provide specific instructions to institutions or IRBs on how to set up their own rules for continuing review within the framework of the regulations. To ensure adequate protection of the rights and welfare of research subjects, institutions and IRBs may impose greater or more detailed standards of protection for human subjects depending upon the nature or location of the study, the degree of risk involved to the subject population, and other factors.

Investigators must also report to the IRB planned changes in the conduct of the study, since these may affect the protection of human subjects. Minor changes proposed for previously approved research may be reviewed in an expedited manner prior to the scheduled continuing review date

Continued—

Figure 5b. OPRR Reports, 95–01 *(continued)*

in accordance with Section 46.110. When a proposed change in a research study is not minor, then the IRB must review and approve changes at a convened meeting before changes can be implemented. The only exception is the rare circumstance in which a change is necessary to eliminate apparent immediate hazards to the research subjects. In this case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with protection of human subjects. Unanticipated risks to subjects or new information that may affect the risk/benefit assessment must be promptly reported to, and reviewed by, the IRB to ensure adequate protection of human subjects.

The regulations at Section 46.111 set forth the criteria to be satisfied if an IRB is to approve research. These include determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The review criteria at Section 46.111 are a requirement during continuing review just as they are in initial review.

In conducting continuing review, the IRB should review, at a minimum, the protocol and any amendments as well as a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any: adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research; (c) a summary of any recent literature, findings, or other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB.

Review of the currently approved consent document must ensure that the information is still accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in accordance with Section 46.116(b)(5). Review of currently approved or proposed consent documents must occur during the scheduled continuing review of research by the IRB, but may be done more frequently if new information becomes available.

Institutions must make investigators aware of the IRB's policies and procedures concerning reporting and continuing review requirements. The IRB's written procedures pertaining to continuing review should be distributed throughout the institution to ensure that all those involved in research activities understand their individual responsibilities.

In summary, in approving the continuation of ongoing research, an IRB attests to its satisfaction that the research continues to be conducted in accord with all relevant provisions of 45 CFR 46. Please examine your institutional and IRB practices to ensure this.

Sincerely,

Gary B. Ellis, Ph.D.
Director
Office for Protection from Research Risks

C. Project/Protocol Review Considerations

In reviewing project/protocol proposals, the IRB must consider the following:

Criteria for Approval of Proposed Research

- *Risks to subjects are minimized* by using procedures that are consistent with sound research design and do not unnecessarily expose subjects to risk and, wherever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

- *Risks to subjects are reasonable in relation to anticipated benefits,* if any, to subjects and the importance of knowledge that may reasonably be expected to result.

- *Selection of subjects is equitable,* taking into account the purposes of the research and the setting in which the research will be conducted. Consideration is given to inclusion of diverse groups of subjects (e.g., age, gender, ethnic background, pregnancy), and the rationale for selection is documented.

- *Informed consent is sought* from each prospective subject (or the subject's legally authorized representative), in accordance with DOE regulations.

- Informed consent is appropriately documented, in accordance with DOE regulations.

- When appropriate, the research plan makes adequate provision for monitoring the collected data to ensure the safety of subjects.

- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- When some or all of the subjects are likely to be vulnerable to coercion or undue influence—such as pregnant women, employees, economically or educationally disadvantaged persons, children, prisoners, or mentally disabled persons—additional safeguards are included in the research to protect the rights and welfare of those subjects.

Evaluation of the Nature and Purpose of the Research

- What is the purpose/overall objectives of the research?

- Does the proposal contain sufficient background information regarding the results of previous studies, including animal or clinical studies, to determine the balance between risks and benefits?

- Is the research controversial and could it potentially generate public concern? If so, should any special recommendations be implemented?

- Are there any potential legal problems or increased investigator/institutional liability associated with the research? If so, should any special safeguards be suggested?

Evaluation of the Risks

A risk is a potential harm (injury) associated with the research that a reasonable person in the subject's position would be likely to consider injurious. Risks can be categorized as physical, psychological, sociological, economic, and legal.

- What are the potential risks, discomforts, or inconveniences associated with the research?

- What is the overall risk classification: less than minimal, minimal, greater than minimal, or life-threatening?

> ***Risk***—*The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study.*

- What is the estimated probability, severity, average duration, and reversibility of any given harm?

- Have adequate safeguards been adopted to minimize to the greatest possible extent the probability of occurrence and the magnitude of the risks?

- What steps will be taken to treat a subject who may suffer an injury?

Evaluation of the Benefits

- What are the potential direct benefits, if any, to the subject? Are these potential benefits maximized to the greatest possible extent?

- What are the potential benefits to society (or some subset)? Are these potential benefits maximized to the greatest possible extent?

> ***Benefit***—*A valued or desired outcome; an advantage; something that promotes or protects well-being.*

Evaluation of the Risk/Benefit Relationship

- Is the potential risk to the subject outweighed or balanced by the potential benefit to the subject and/or by the potential benefit to society?

- In research involving children, pregnant women, fetuses, and prisoners, is the risk/benefit relationship acceptable according to the requirements of 45 CFR 46, Subparts B, C, or D?

Evaluation of the Subject Populations

- What are the inclusion/exclusion criteria (for example, sex, age, health status, number of subjects)?
- Is the proposed subject population(s) appropriate for the goals of the study?
- Is the selection of subjects as equitable as possible, considering any restrictions imposed by justifiable inclusion/exclusion criteria?
- Will any particular physiological, health, psychological, or sociological characteristics of the subject population pose special medical, ethical, or legal problems? Have appropriate steps been taken to minimize these potential problems?
- Is the inclusion of a vulnerable subject population (such as children, pregnant women, fetuses, prisoners, elderly persons, the mentally incompetent, the terminally ill) justified and in compliance with 45 CFR 46?

Evaluation of Subject Recruitment

- Is the method used to identify a particular subject population ethically and legally acceptable?
- Is the process used to recruit potential subjects appropriate and free of coercion?
- Are the advertisements used to recruit subjects acceptable?

Evaluation of the Process of Obtaining Informed Consent

- Who will solicit informed consent from the subject?
- Will the timing of and setting for the process of informed consent be conducive to rational and thoughtful decision-making by the subject without coercion?

Informed Consent—A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventative procedure.

- Should subjects be reeducated at periodic intervals and informed consent again solicited?
- Will the nature of the research or other factors potentially inhibit a subject's desire/ability to withdraw from participation? If so, have appropriate steps been taken to minimize this problem?
- Will the subjects be physically and mentally competent to give informed consent? If not, is there an acceptable alternative procedure established in lieu of participant's consent? *(See 10 CFR 745.116 and 45 CFR 46, Subparts B, C, and D. These regulations are included in Chapter 2 of this handbook.)*

- Should a subject advocate or other individual be present during the consent process?

- If a waiver of some or all of the elements of informed consent is requested, does the nature and/or importance of the research justify such a waiver? Is the waiver in compliance with Federal regulations? NOTE: Neither IRB review nor informed consent may be waived for classified research.

Evaluation of Research Data Processing and Storage

- How will the research data be stored and maintained?

- How sensitive will the research data be?

- Will the investigator provide information about subjects to other individuals and/or agencies? If so, is this ethically and legally acceptable?

- To what extent would a breach of confidentiality or invasion of privacy constitute a harm to subjects?

- Are there adequate provisions to protect participants from the risks of breach of confidentiality and invasion of privacy?

- Should a statutory shield against subpoena of research records be obtained (available for research on mental disorders and drug and alcohol abuse)?

Additional Monitoring

- Should the research be reviewed by the IRB more than once a year? If so, when and how should this review be accomplished?

D. Incentives for Participation

Introduction

Each year, thousands of individuals are paid for participating in biomedical and behavioral research funded either by Federal agencies or private institutions. Although payments are usually monetary, both patients and normal healthy volunteers may be offered other rewards in lieu of or in addition to money, such as free medical care. Regardless of the form of remuneration, the issues for IRBs remain the same. IRBs must consider whether paid (or otherwise rewarded) participants in research are recruited fairly, informed adequately, and paid (or rewarded) appropriately. Taking into consideration the subject's medical, employment, and educational status and financial, emotional, and community resources, the IRB must determine whether the rewards offered for participation in research constitute undue inducement.

Taking into consideration the subject's medical, employment, and educational status and financial, emotional, and community resources, the IRB must determine whether the rewards offered for participation in research constitute undue inducement.

Overview

Federal regulations governing research with human subjects contain no specific guidance for IRB review of payment practices. One of the primary responsibilities of IRBs, however, is to ensure that a subject's decision to participate in research will be truly voluntary and that consent will be sought "only under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence" (45 CFR 46.116 and 12 CFR 50.200).

Clear cases of coercion (i.e., actual threats) are readily identifiable; it is more difficult to recognize undue inducement. An offer one could not refuse is essentially coercive (or "undue"). This is of particular concern when employees or students are recruited. Undue inducements may be troublesome because offers that are too attractive may—

- Blind prospective subjects to the risks or impair their ability to exercise proper judgment.
- Prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling—or continuing—as participants in a research project.

IRB Considerations

IRBs must ensure that prospective subjects realize that their participation is voluntary and choosing not to participate will not adversely affect their relationship with the institution or its staff in any way. To make this determination, IRBs should know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

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. Institutions may consider a random or "lottery" selection from a volunteer pool to eliminate peer pressure and to promote fair selection of subjects. Institutions should ensure that the consent form contains a detailed account of the terms of payment, including a description of the conditions under which a subject would receive partial or no payment (for example, what will happen if they withdraw partway through the research).

Determining the appropriateness of the incentive is another matter. For research that requires subjects to undergo only minor inconvenience or discomfort, a modest payment will usually be adequate. Reimbursement for travel, babysitting, and so forth may also be provided. In more complex research projects, IRBs tend to base their assessment on the prevailing payment practices within their institution or general locale. Volunteers are often compensated for their participation according to an established fee schedule, based upon the complexity of the study, the type and number of procedures to be performed, the time involved, and the 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, IRBs may need to become familiar with the accepted standards within their community as well as the anticipated discomforts and inconveniences involved in a particular study to judge appropriateness of payments. Some institutions have 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).

One of the most perplexing problems for IRBs is how to assess the appropriateness of payment offers for experiments that involve the assumption of risk or significant discomfort.

One of the most perplexing problems for IRBs is how to assess the appropriateness of payment offers for experiments that involve the assumption of risk or significant discomfort. On a practical level, it is probably impossible for an IRB to determine what amount of money or type of reward would unduly influence a particular individual to accept a given degree of risk. Although our society generally accepts the premise that those assuming risk deserve reward, the application of this rule in establishing payment for subjects in biomedical and behavioral experiments is still being debated. This is a matter each institution must address in formulating its policies.

IRB members tend to approach the problem of assuming risk for pay from one of two positions. One side argues that normal healthy volunteers are able to exercise free choice and that, since judging the acceptability of risk and weighing the benefits is a very personal matter, IRBs should refrain from imposing their own views on potential subjects. IRB responsibility should be confined to ensuring that consent is properly informed. Other IRB members 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. Free health care for those with limited resources and major medical problems may be a significant inducement to participate in research (even if it is nontherapeutic). There is no consensus as to whether this is unacceptable. In assessing this potential problem, IRBs might consider whether only the destitute agree to volunteer or if people who can obtain good medical care on their own agree to participate as well. IRBs may need to monitor subject recruitment in order to make such determinations.

Points To Consider

- Are all conditions in keeping with standards for voluntary and informed consent?
- Are the incentives offered reasonable, based upon the complexities and inconveniences of the study and the particular subject population?
- Are there special standards that the IRB ought to apply to the review of research in which volunteers are asked to assume significant risk?

Investigator Responsibilities and Procedures

A. Introduction

***Principal Investigator**—The scientist or scholar with primary responsibility for the design and conduct of a research project.*

As the person who designs and implements the research proposal and often interacts personally with research participants, the principal investigator (PI) plays a vital role in the protection of human subjects. Principal investigators must be familiar and comply with the Federal regulations and U.S. Department of Energy (DOE) orders established to protect the rights and welfare of human research subjects. *(Reprints of the applicable regulations and orders are found in Chapter 2 of this handbook.)* Principal investigators must also be familiar with and have a copy of their institution's assurance of compliance with the regulations. *(See Chapter 4.)* Research projects that will involve human participants should be clearly identified as human subjects research as early as possible in proposal preparation and review process. The type of research that falls into this category, however, is not necessarily obvious. Human subjects research includes a broader range of research than many investigators and program managers realize. *(See Chapter 1 of this handbook for specific guidance on identifying human subjects research.)* When in doubt, principal investigators should seek guidance from their institutional human subjects point of contact or their Institutional Review Board (IRB) Administrator. *(See Chapter 14 for a list of points of contact at DOE laboratories, operations offices, and program offices.)*

This chapter lists investigator responsibilities in the preparation, review, and implementation of a research proposal to involve human subjects. A flow chart displaying the proposal preparation and review process is included as a quick reference *(Figure 6c)*. Also provided is specific guidance on informed consent. Investigators should keep in mind that informed consent is a *process*, not just a document. Every step should be taken to ensure that subjects have a thorough understanding of the purpose, procedures, risks (if any), and possible benefits of the study in which they will participate. Several sample documents, including a sample informed consent document and a human subjects' bill of rights, are included in this chapter to further guide the investigator in the adequate preparation and implementation of research proposals.

B. Proposal Preparation and Review

Following are the PI's responsibilities associated with research projects involving human subjects:

Reference Materials Included in This Section

- Sample IRB Review Request Form (Figure 6a).
- Sample Request for Continuing Review Form (Figure 6b).
- Human Studies Review Process Flow Chart (Figure 6c).

Obtaining Management Approval of Proposal

- The PI writes a proposal (or an amendment to an existing proposal or to a funded research project) to do research that will involve human subjects or use human data, records, pathological specimens, or diagnostic specimens.
- The PI obtains line management concurrence that it is necessary to involve human subjects in the research.
- The PI obtains a review and approval of the proposal for scientific merit (by line management, research committee, or whatever approval mechanism exists at local site).
- The PI and/or PI's manager make a preliminary determination about whether the research requires review by the full board of the IRB, qualifies for expedited IRB review, or is entirely exempt from IRB review. (The PI should contact the IRB Administrator for guidance.) *The IRB makes the final determination of the type of review required.*

Preparing and Submitting a Proposal Review Package

The PI submits to the IRB Administrator a proposal package that includes *copies* of each of the following:

- A signed IRB Review Request Form or similar memo. *(See Figure 6a for an example of the kinds of information that should be included.)*
- A 1- or 2-page abstract of the proposed research (including a description of risks and potential benefits of the research to the individual human subjects).
- A complete research proposal, including provisions for the protection of human subjects in accordance with DOE regulations and all other applicable laws and regulations.
- Sample(s) of proposed informed consent form(s) or proposed research subject information forms.
- Any proposed advertisement for human volunteers.

- Approval from IRB of institutions participating in cooperative research or participating subrecipients. (*See Chapter 8 for guidance.*)

- IRB approval letter from participating international entities. (*See Chapter 9 for guidance.*)

Possible Interactions

After the PI has submitted the proposal package, the PI may be requested to attend an IRB meeting to answer questions regarding the research. The PI may need to modify parts of the research proposal to meet certain conditions for IRB approval.

Obtaining Approval From and Complying With IRB Decisions

The PI complies with all IRB decisions, conditions, and requirements regarding the research proposal and the consent document. (The IRB has the continuing right to contact subjects directly to evaluate the investigator's compliance with the IRB's approval.)

Completing Requirements Prior to Involvement of Human Subjects

Prior to involving any human subject, the PI is able to show that—

- The proposed research and consent forms have been reviewed and approved by the IRB.

- Informed consent of the subjects or their legally authorized representatives has been obtained.

- Certification of the IRB and the institution approval of the proposed research have been signed. If the PI's institution does not have a Multiple Project Assurance (MPA), a Single Project Assurance (SPA) has been submitted to the DOE Office of Health and Environmental Research (OHER, ER-70), for approval. SPA approval from OHER must be obtained before human subjects become involved in the new project.

- A copy of the approved assurance document has been given to each investigator conducting research covered by the assurance document.

Obtaining Informed Consent and Retaining Consent Forms

- Prior to involving volunteers, the PI explains the informed consent process and encourages the subject to ask questions. The PI has each research subject read and sign an informed consent document and gives each research subject a copy of the signed consent form. The consent form may be read to the subject or to the subject's representative, but an oral presentation must be witnessed, and the witness must also sign the consent form.

  NOTE: If research involves no more than minimal risk, the requirement to *document* informed consent may be waived under certain circumstances by the IRB.

- The PI provides for appropriate retention of signed consent forms (to protect privacy) for at least 3 years after termination of the research project. These forms must be accessible for inspection and copying by authorized representatives of DOE.

- The process does not preempt any Federal, state, or local laws about informed consent or limit the authority of a physician to provide emergency medical care.

Reporting Changes, Injuries/Problems, and Progress to the IRB

The PI immediately reports to the IRB—

- Any proposed changes in previously approved proposal or consent form.

  NOTE: The IRB chairperson or another designated member can approve minor changes by expedited review. (The consent form must be reviewed at least annually by the IRB; date of review should be marked on the consent form.)

- Any injuries to human subjects, any unanticipated problems that involve risks to human subjects or others, or any serious or continuing noncompliance with the requirements of the approved assurance document or determinations of the IRB.

Research progress is reported to the IRB at least once a year (or more often, if required by the IRB), and a summary is provided upon completion of the project.

Submitting a Supplement to an Original Proposal

The PI submits a supplement to the original proposal when proposing to—

- Involve human subjects in research that previously had undefined plans for the involvement of human subjects, or involve human subjects in research that previously had no intention of involving human subjects. Neither category of research may involve any human subject until the supplement is reviewed and approved as indicated above.

- Significantly change approved research involving human subjects, unless the change is necessary to eliminate an apparent immediate hazard to the human subject(s).

Submitting a Continuation Request

The PI submits a request for continuation of approval of ongoing research at least 1 month prior to the expiration date of the existing IRB approval. *(See Figure 6b.)*

Figure 6a. Sample IRB Review Request Form

Name of Institution

For IRB Use Only
ORA or IRB Administrator Approval:
IRB #:
Type Review:

Application for Institutional Review Board (IRB) Review and Approval

Please type the information or print in BLACK INK. Return application, protocol, and consent form to your Office of Research Administration (ORA) to get permission from your institution to do the research. Bring the proposal, consent form, and application form to the IRB office. If you are not an employee at the institution where the research will be conducted, call the IRB office about signing the "Investigator's Agreement."

Investigators' Names: _____

_____

Investigators not institution employees: _____

_____

Research Site: _____

Collaborating Institutions: _____

_____

Research Project Title: _____

_____

_____

Project/Protocol #: _____ Consent Form Code: _____

Number of subjects: _____ Duration of study: _____

This research project involves vulnerable groups: ❑ No ❑ Yes

If yes, indicate group:

❑ Minors
❑ Economically or educationally disadvantaged
❑ Pregnant women, fetuses, human ova *in vitro* fertilization
❑ Other. *Please specify.* _____
❑ Prisoners
❑ Cognitively impaired
❑ Psychiatric patients

Recommended Review Type:

❑ Exempt ❑ Expedited Review ❑ Full Board Review

Continued—

Figure 6a. Sample IRB Review Request Form *(continued)*

Proposed research: _____

Synopsis as explained to your patient/subject. (Include procedures to be done, samples to be obtained, drugs, exercise, etc.): _____

Foreseeable risks or discomforts: _____

Benefits to subject: _____

Other pertinent information: _____

Figure 6b. Sample Request for Continuing Review Form

Institutional Review Board
(Name of Institution)
Research Involving Human Subjects
Continuing Review

Project Title: _____

Principal Investigator: _____

Group _____ Address _____

1. Review Requirement: Annual ___ Other ___

2. Will this project be conducted during the next review period?

3. Have there been any changes in protocol or informed consent since the last review, or are any such changes planned? If so, please describe.

4. Have any injuries to human subjects or unanticipated problems involving risks to human subjects occurred? If so, please describe.

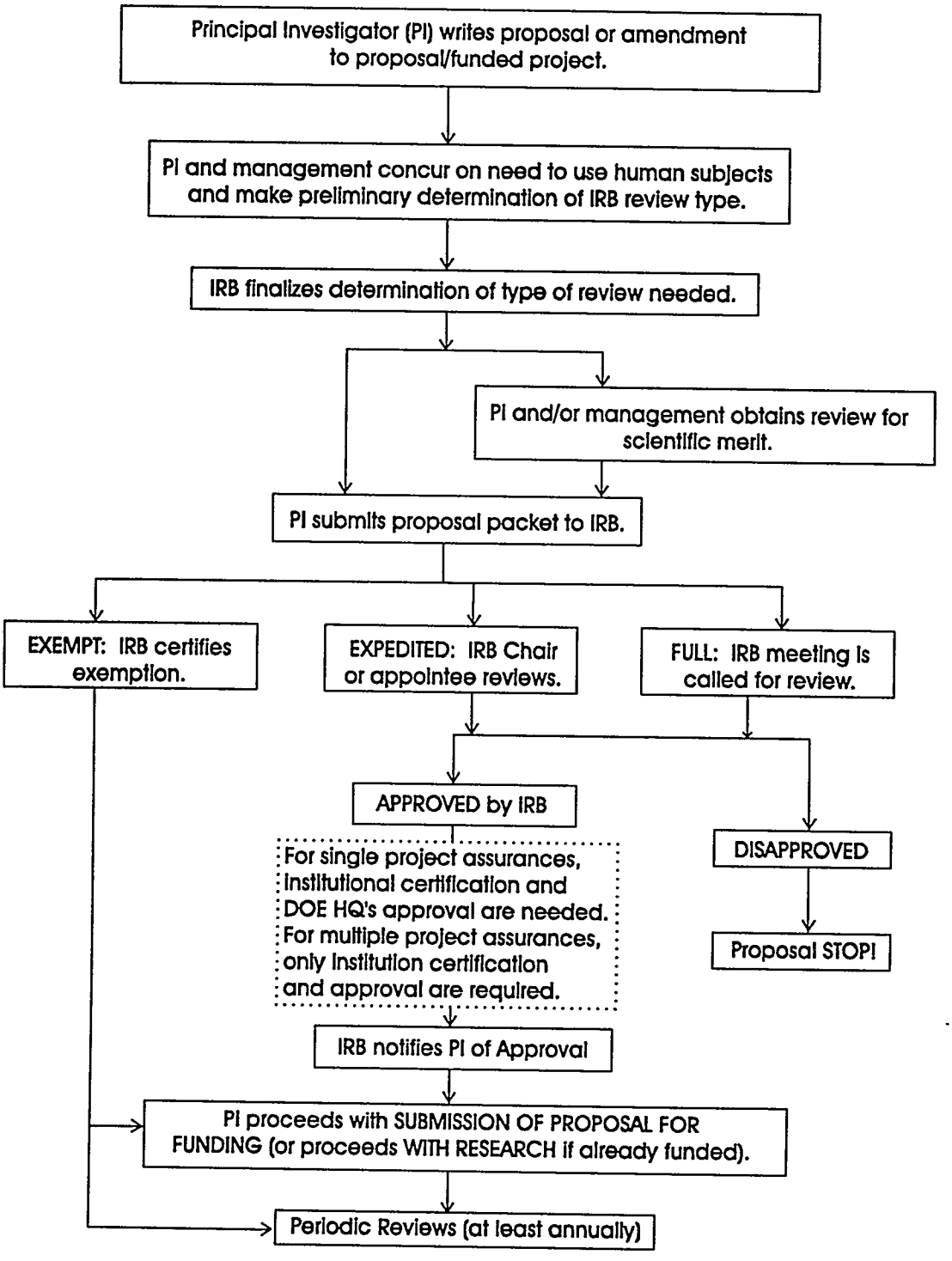
_____
Signature, Principal Investigator (Date)

_____
IRB Chair (Date)

Return to: Designee of the Institution's Institutional Review Board

Figure 6c. Human Studies Review Process Flow Chart

With the exception of DOE headquarters approval, this process applies to both MPA and SPA institutions.



C. Informed Consent Preparation

> ***Informed Consent***—*A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventative procedure.*

Informed consent is a *process,* not just a form. It is critical that information is presented so that persons can voluntarily decide whether or not to participate as research subjects. Informed consent is a fundamental mechanism to ensure respect for persons by seeking thoughtful consent to a voluntary act. Informed consent procedures should strive to educate and inform research subjects; however, these procedures (especially explanation of the study's purpose, duration, experimental procedures, alternatives, risk, and benefits) must be written in a language that participants can understand. The written document is the basis for consent and gives the subject material for future reference. The consent form must be revised if deficiencies are noted or if additional information becomes available. The following are standard informed consent document requirements that may be presented in either a written or an oral format. *[For additional guidance, see OPRR Reports 93–03 (Figure 6d).]*

Informed Consent Document Requirements

(See Figure 6e for a sample research subject consent form.)

Language

A consent document must be written in nontechnical language (e.g., the level of writing normally found in a newspaper or general circulation magazine) that research subjects can understand. The PI should avoid jargon and define scientific/medical terms as clearly and plainly as possible. Informed consent, whether oral or written, may not include exculpatory language through which the subject or the authorized representative waives or appears to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, and the institution or the institution's employees from liability for negligence.

Reference Materials Included In This Section

- OPRR Reports, 93–03 (Figure 6d).
- Sample Research Subject Consent Form (Figure 6e).
- Sample Human Subjects Bill of Rights (Figure 6f).

Required Elements of a Consent Document

A consent document must contain the following:

- A statement that the study involves research.
- An explanation of the purpose of the research.
- A statement of the expected duration of the subject's participation.
- A description of the procedures to be followed.

- Identification of any procedures that are experimental.
- A description of foreseeable risks or discomforts.
- A description of benefits to the subject or to others.
- A disclosure of appropriate alternative procedures or courses of treatment.
- A description of the extent to which records identifying the subject will be confidential.
- For research involving more than minimal risk, an explanation of any compensation and/or medical treatment available if injury or accident occurs.
- An explanation of whom to contact—
  - — For answers to pertinent questions about the research.
  - — For answers about subject's rights.
  - — In the event of a research-related injury to the subject.
- A statement that participation is voluntary and that refusal to participate will not involve penalty or loss of benefits to which the subject is entitled.
- A statement that the subject may discontinue participation at any time without penalty or loss of benefits.

The process of obtaining informed consent must comply with the requirements of 10 CFR 745.116. The documentation of informed consent must comply with 10 CFR 745.117.

Added Elements of a Consent Document

When appropriate, the consent document may include any of the following elements:

- A statement that a particular treatment or procedure may involve risks that are currently unforeseeable (e.g., to the subject or to the embryo or fetus). *(See section on Unforeseen Risk in Chapter 10.)*
- A summary of the circumstances under which the subject's participation may be terminated by the PI without the subject's consent.
- A description of additional costs to the subject resulting from participation in research.
- A description of the consequences of the subject's decision to withdraw from research and procedures for termination of participation by the subject.
- A statement that significant new findings will be provided to the subject.
- A statement about the approximate number of subjects involved in the study.
- Identification of the agency supporting the proposed research. This may be a significant element of information to include in the informed consent process for classified research projects.

Exceptions

The Food and Drug Administration (FDA) has some exceptions to requirements for informed consent:

1. Obtaining informed consent may be waived if both the investigator and a physician who are not otherwise participating in the clinical investigation certify in writing all of the following:

   a. Subject is in life-threatening situation necessitating use of test article.

   b. Consent cannot be obtained because of an inability to communicate with or obtain consent from the subject.

   c. Time is not sufficient to obtain consent from subject's legal representative.

   d. No alternative generally approved method is available.

2. If immediate use of the test article is required to save the life of the subject and time is not sufficient to save the life of the subject and time is not sufficient to obtain independent determination by another physician, a determination by the investigator shall be made.

3. This determination is to be reviewed and evaluated in writing by a physician who is not participating in the investigation within 5 days after use of article.

4. The documentation required in 1, 2, or 3 above must be submitted to the IRB within 5 working days after use of test article.

Exceptions to *documenting* informed consent are as follows:

1. IRB may waive requirement to obtain a signed consent form from subjects if—

   a. The only record linking the subject and the research would be the consent document and the principal risk would be harm resulting from breach of confidentiality; each subject must be asked whether subject wants documentation; or

   b. The research presents no more than minimal risk and involves no procedures for which written consent is normally required.

2. In cases where documentation is waived, the IRB may require investigator to provide subject with written statement regarding the research.

NOTE: 1a and 1b under exceptions to *documenting* informed consent are part of the Common Rule. *FDA, however, does not permit exception 1a.* As this handbook went to press, FDA had proposed to amend its current informed consent regulations with respect to emergency research. *For more information, see Emergency/Critical Medical Care in Chapter 10 and FDA's proposed rule in Chapter 15.*

Figure 6d. OPRR Reports, 93–03

Number 93–03
Human Subject Protections

OPRR Reports

NIH PHS HHS

August 12, 1993

Subject: Informed Consent—Legally Effective and Prospectively Obtained

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) Chairs throughout the country. Its purpose is to reiterate the mandate for obtaining legally effective informed consent prospectively from each research subject or the subject's legally authorized representative. This requirement is applicable to all research activities conducted or supported by the Department of Health and Human Services (HHS) and is stipulated in the HHS regulations for the protection of human research subjects (45 CFR 46.116). The requirement is equally applicable to research which is not supported or conducted by HHS, if the research is carried out in accord with a Multiple Project Assurance (MPA) approved by the Office for Protection for Research Risks (OPRR), and no alternative procedures were presented and approved in the applicable MPA.

There are only two circumstances under which the regulations give IRBs authority to waive the required consent. The first waiver authority is applicable only to research activities designed to study certain aspects of public benefit or service programs; the conditions under which this waiver may be authorized by an IRB are detailed at 45 CFR 46.116(c). The second waiver authority is described at 45 CFR 46.116(d) as follows:

> 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.

Continued—

Figure 6d. OPRR Reports, 93–03 *(continued)*

Recently, we have become aware of the use of a consent procedure referred to as "deferred consent" or "ratification." Informed consent procedures which provide for other than legally effective and prospectively obtained consent fail to constitute informed consent under the HHS regulations for the protection of human research subjects. Similarly, the waiving of informed consent, using a method other than that requiring the IRB findings and IRB documentation specified at 45 CFR 46.116(c) or (d) is not in compliance with the regulations.

I urge your careful review of these requirements as they may apply to your institution's and your IRB's actions and procedures. If you have any questions as you carry out this task, please contact Bill Dommel, OPRR's Senior Policy Advisor, at (301) 496-7005.

Gary B. Ellis, Ph.D.
Director
Office for Protection from
Research Risks

Figure 6e. Sample Research Subject Consent Form

RESEARCH SUBJECT CONSENT FORM

Prospective research subject—Read this consent form carefully and ask as many questions as you like before you decide whether you want to participate in this research project.

Title: _____

Sponsor: _____

Principal Investigator/Department: _____

Other Investigator(s)/Department(s): _____

Organization/Location: _____

1. PURPOSE OF RESEARCH STUDY

"You are being invited to participate in a research study designed to . . . "

- Include 3–5 sentences written in nontechnical language.
- Define what is unique/different about this project.
- If possible, indicate population and number of people to be studied.

2. PROCEDURE

- Describe procedures to be followed.
- Identify any procedures that are experimental.
- Define expected duration of subject's participation.
- Indicate type/frequency of monitoring during/after study.

3. POSSIBLE RISKS/DISCOMFORTS

- Describe known or possible risks.
- Indicate any special risks to women of childbearing age; if relevant, state that study may involve risks that are currently unforeseeable, e.g., to developing fetus.
- If subject's participation will continue over time, state: "Any new information developed during the study that may affect your willingness to continue participation will be communicated to you."

4. POSSIBLE BENEFITS AND COMPENSATION

- If the research is not of direct benefit to participant, explain possible benefits to others.
- Explain any financial compensation involved or state; "There is no financial compensation (other than your normal salary) for your participation in this research project."

Continued—

Figure 6e. Sample Research Subject Consent Form *(continued)*

5. AVAILABLE MEDICAL TREATMENT FOR ADVERSE EXPERIENCES

"For employees: If you are injured as a direct result of taking part in this research study, emergency medical care will be provided by _____ medical staff or by transporting you to your personal doctor or medical center. Normal benefits consistent with policies and practices remain available to _____ employees."

"For non-employees: If you are injured as a direct result of taking part in this research study, emergency medical care will be provided by _____ medical staff or by transporting you to your personal doctor or medical center. Neither _____[institution]_____ nor the Federal government will be able to provide you with long-term medical treatment or financial compensation except as may be provided through whatever remedies are normally available at law."

[6. AVAILABLE ALTERNATIVE COURSES OF TREATMENT ——— if relevant, then change following numbers.]

6. CONFIDENTIALITY

"Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you."

"However, any records or data obtained as a result of your participation in this study may be inspected by the sponsor, by any relevant governmental agency (e.g., U.S. Department of Energy), by the Institutional Review Board or by the persons conducting this study, provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except as otherwise authorized or required by law."

7. TERMINATION OF STUDY

"You are free to choose whether or not to participate in this study, and there is no penalty or loss of benefits if you decide not to participate. You are also free to leave the study at any time without penalty or loss of benefits, but if you do so you must notify the Principal Investigator."

"Your participation in this study may be ended by the Principal Investigator at any time. The sponsor reserves the right to terminate the study at any time."

Continued—

Figure 6e. Sample Research Subject Consent Form *(continued)*

8. AVAILABLE SOURCES OF INFORMATION

"Any questions you may have about this study will be answered by the Principal Investigator,

_____, at

_____[phone #]_____."

"Any questions you may have about your rights as a research subject will be answered by

_____, at

_____[phone#]_____."

"In case of a research-related emergency, you should call _____[emergency number]_____ or, from home during evenings or weekends, call _____."

9. AUTHORIZATION

"I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study. I further understand that nothing in this consent form is intended to preempt any applicable Federal, state, or local laws regarding informed consent."

_____

Participant Name (Please Print)

_____

Participant Signature Date

_____

Investigator Signature Date

_____

Witness Signature Date

D. Consideration of Subjects' Rights

The Common Rule requires that the *rights*, as well as the welfare, of human research subjects be protected. California law requires that any person asked to take part as a subject in research involving a medical experiment or any person asked to consent to such participation on behalf of another is entitled to receive a list of rights in a language in which the person is fluent. Other states may also have similar requirements. Institutions should check with their local authorities regarding specific requirements for their area.

DOE encourages institutions that conduct human subjects research to have a human subjects' bill of rights either posted at their facility or available as a handout. *(See Figure 6f.)* This document tells subjects what they should expect as participants in research and what type of information to expect in the informed consent process. It serves as a guide, to help subjects know what questions they should ask about the research before they agree to participate. The human subjects' bill of rights should be provided in the language of the subjects who will be participating in the research. Since it is a standard institutional document that does not change from project to project, translation expenses and complications are minimal.

Figure 6f. Sample Human Subjects Bill of Rights

[Institution]
Experimental Subject's Bill of Rights

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject, I have the following rights:

1. To be told what the study is trying to find out.
2. To be told what will happen to me and whether any of the procedures, drugs, or devices differ from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes.
4. To be told if I can expect any benefit from participating and, if so, what the benefit might be.
5. To be told of the other choices I have and how they may be better or worse than being in the study.
6. To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study.
7. To be told what sort of medical treatment is available if any complications arise.
8. To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study.
9. To receive a copy of the signed and dated consent form.
10. To be free of pressure when considering whether I wish to agree to be in the study.

If I have other questions, I should ask the researcher or the research assistant. In addition, I may contact the Committee on Human Research, which is concerned with protection of volunteers in research projects. I may reach the committee office by calling _____[telephone number]_____ 8:00 a.m. to 5:00 p.m., Monday through Friday, or by writing to the Committee on Human Research, Box _____, University of _____. Call _____ for information on translations.

Data Protection

A. Introduction

This chapter addresses three topics:

- Classified or sensitive research (Section B).
- Proprietary concerns and the Freedom of Information Act (FOIA) (Section C).
- Legal aspects of the use of personally identifiable human subjects data (Section D).

Section B emphasizes that classified or sensitive projects are *not* exempt from institutional review board (IRB) review, and it identifies two alternatives that meet this requirement, normal review and classified/sensitive review. It discusses the circumstances that determine which type of review is necessary for a given project and summarizes the procedures to be used in each type of review.

Section C encourages IRBs to minimize their acquisition of proprietary information and obtain such information only to the extent necessary to protect the well-being of human subjects. Federal law protects certain proprietary information and even imposes criminal penalties for its disclosure under some circumstances. Unless prohibited by legal requirements or the need to protect human subjects' privacy, however, the Department of Energy (DOE) generally chooses to disclose information. (Figure 7a presents DOE Order 1700.1, which establishes the Department's Freedom of Information Program under FOIA.) The situation is further complicated because Federal regulations, State laws, and the obligations imposed by individual contracts mean that requirements can vary from state to state, institution to institution, and project to project.

Section D presents highlights of Federal and state laws bearing on the use of personally identifiable human subjects data. It notes, for example, that FOIA permits DOE not to disclose private information, but does not require nondisclosure. It is DOE policy not to release personally identifiable data except with the consent of the subjects' or their surviving family members or pursuant to court order. The section also points out that with few exceptions, state statutes require the considered, orderly management and use of personally identifiable information; they do not absolutely bar disclosure of the information.

B. Classified or Sensitive Research

Institutional Review Board (IRB) Review of Classified or Sensitive Research

Research projects employing human volunteers may be deemed classified or sensitive on the basis of national security considerations. Classified or sensitive projects are *not* exempt from review by the institution's IRB. Review of such projects may be done according to either of the following procedures.

Normal Review

Proposed research is reviewed at a regular meeting of the institution's IRB in an unsecured environment without disclosure of classified information. This form of review of classified or sensitive research may be employed only after the security-cleared chairperson (or other security-cleared designated reviewer) of the IRB has determined that—

- The research will be accurately and comprehensively described to the IRB.
- No classified or sensitive information is relevant to the protection of human subjects.

Normal IRB review is preferred if there is any possible way to review the consent procedure and protection of human volunteers without revealing specific classified details of the research. Also, all paperwork submitted to the IRB must be unclassified. If this is not possible, the principal investigator (PI) should contact the IRB Administrator before submitting any paperwork to ensure that classified or sensitive information is not compromised.

Classified/Sensitive Review

If the proposed research cannot be reviewed in accord with the above conditions for normal review, it is reviewed at a meeting of the institution's IRB conducted in a secure environment. As required by the Federal Common Rule and the institution's U.S. Department of Energy (DOE) assurance, a majority of the members of the IRB, including at least one nonscientist, must be present at this meeting. Each member of the IRB, including the community member, must have the appropriate security clearance.

NOTE: Identification of the agency supporting the proposed research may be a meaningful element of information that should be provided in the informed consent process where appropriate. *(See Informed Consent Preparation in Chapter 6.)* If such information is, itself, classified or sensitive, then the identity may be undisclosed to the IRB provided that the Laboratory Director or designee specifically approves withholding such information.

C. Proprietary Concerns and the Freedom of Information Act (FOIA)

Reference Material Included in This Section

- DOE Order 1700.1 (Figure 7a).

The laws, regulations, DOE Orders, and contractual and programmatic requirements pertaining to the definition of proprietary information and how to protect it from unauthorized disclosure come from a multitude of sources. Federal requirements, state statutes, and contractual obligations interact to create a fabric that differs from institution to institution and from project to project.

IRBs should endeavor to provide the highest degree of confidence that proprietary information will be appropriately protected, consistent with legal and contractual requirements. For example, information developed under a Cooperative Research and Development Agreement (CRADA) can be protected for up to 5 years under the authority of the National Competitiveness Technology Transfer Act of 1989 (NCTTA). Indeed, Federal law imposes criminal penalties on Government employees who divulge proprietary business information under 18 USC 1905. Other statutory authority available to DOE and its contractors permits DOE to deny requests for proprietary information under Exemption 4 of FOIA, 5 USC 552, as amended. However, except where such statutory authority *requires* the protection of proprietary information, DOE has chosen to release information where the exemption is merely discretionary, unless disclosure will produce a foreseeable harm.

Information about individuals that is protected by the Privacy Act of 1974, 5 USC 552a will generally be protected from disclosure under FOIA. The Privacy Act prohibits disclosure of most privacy-related information. Moreover, according to DOE policy, information that contains sensitive, personally identifiable human subjects data will be redacted before being released to the public, unless DOE is directed to release it by a court order or given permission to do so by the individuals identified or, in some cases, by their surviving family members.

In light of the above, IRBs should work together with contractor management and third-party participants to obtain proprietary information only to the extent necessary to protect the well-being of human subjects. Proprietary information that is provided to the IRB, unless otherwise protected by law, may be subject to disclosure.

DOE contractors are contractually obligated to protect proprietary information in their possession in accordance with any restrictive legend on such material pursuant to the standard Rights in Technical Data clause from section 52.227-14 of the Federal Acquisition Regulations. DOE contractors may have their own proprietary interests in information developed at private expense pursuant to their DOE-approved technology transfer programs. DOE does not acquire ownership of contractor documents unless the funding agreement so provides, and unless and until the documents are actually furnished to DOE. Generally speaking, IRB records are treated as though they are agency records, and disclosure will generally be authorized by DOE.

Furthermore, even if *public* release is not authorized, DOE will normally permit others within the Federal Government to have access to proprietary information in its possession to carry out any legitimate Government purpose. Therefore, care must be exercised to retain proprietary information only when unavoidable, unless the owner of such proprietary information acknowledges and approves such release.

Other FOIA exemptions, such as for protecting classified information, are discussed in DOE Order 1700.1. *(See Figure 7a.)*

Proprietary Information and the DOE Human Subjects Research Projects Database

Institutions should be sensitive to classified, confidential, or proprietary data when entering projects in the database. All information entered into the database will be made available to the public unless stated otherwise on the database form. *(See Chapter 12.)* It is recommended that data for projects that include confidential or proprietary information be reviewed by secondary parties (e.g., CRADA partners) before being entered into the database.

Withholding of Information From the Database

Information concerning possible patentable inventions in which the United States has an interest can be withheld from public disclosure for a reasonable period of time to allow for the filing of a patent application. This is permitted by 35 USC 205. An appropriate disclaimer for inclusion in the database, in lieu of disclosure of such information, would be—

> The objective of this project is to reduce to practice a (named) invention. Pursuant to 35 USC 205, technical information relating to this invention will not be released until a patent application has been filed.

However, parties other than the United States may own or have an interest in project information considered for inclusion in the database. Data produced under a CRADA would be the property of the party producing it; data produced under a nongovernment-funded Work-for-Others agreement would be owned by the paying sponsor. Statutes other than 35 USC 205 could affect the disclosure or nondisclosure of such information. Because different governing contractual provisions affecting data ownership are used throughout the DOE complex, questions regarding ownership, disclosure, and the appropriate disclaimers to be used in specific cases of nondisclosure should be referred for guidance and/or resolution of Patent Counsel in the cognizant Operations Offices.

Figure 7a. DOE Order 1700.1

U.S. Department of Energy
Washington, D.C.

Order
DOE 1700.1
11-19-79

SUBJECT: FREEDOM OF INFORMATION PROGRAM

1. PURPOSE. To establish guidelines and procedures for the processing of requests made to the Department of Energy (DOE) under the Freedom of Information Act (FOIA).

2. POLICIES.

   a. It is the policy of the Department to make information publicly available to the fullest extent possible. Officers and employees of the Department may furnish to the public informally and without compliance with procedures in this Order, information and records of types which officers and employees of the DOE customarily furnish to the public in the regular performance of their duties.

   b. Information in the possession of the Department will be made available to the public unless it is exempt from mandatory public disclosure pursuant to one or more of the exemption provisions of the FOIA, 5 U.S.C. 552 (Public Law 90-23, as amended) or other applicable statutes.

   c. To the extent permitted by other laws, DOE will make available records which it is authorized to withhold under the FOIA. However, in light of a recent Supreme Court decision,[1] any discretionary release of materials exempt under the fourth exemption and/or 18 U.S.C. 1905 should be coordinated with the Office of General Counsel.

   d. The policies and procedures stated in this Order shall be interpreted so as to be consistent with the Privacy Act of 1974, 5 U.S.C. 552a (Public Law 93-579).

   e. There is no obligation to compile or create a record solely for the purpose of satisfying a request for records.

3. CONTRACTOR RECORDS. Where a contract with the DOE stipulated that any documents relating to work under the contract shall be the property of the Government, such records shall be considered to be agency records and subject to disclosure under the FOIA. However, if a contract does not make such specific provisions, no DOE contractor records shall be considered to be agency records unless and until such time that the DOE acquires possession of the particular contractor documents.

DISTRIBUTION:
All Departmental Elements

INITIATED BY:
Office of Administrative Services

[1] *Chrysler Corp. v. Brown*, 441 U.S. 281 (1979), in which it was held that (1) the Government cannot rely on the FOIA alone as a congressional authorization for a discretionary disclosure of information otherwise covered by an exemption; and (2) the disclosure of the information in question must have been reasonably contemplated by Congress in the statute cited as authority for the release.

D. Legal Aspects of the Use of Personally Identifiable Human Subjects Data

Federal

It is DOE's policy . . . to protect the privacy of individuals and not to release personally identifiable human subjects research data in the absence of the subjects' consent or that of surviving family members, or unless pursuant to court order.

Freedom of Information Act[2]

FOIA is a mandatory disclosure statute with certain exemptions that permit DOE to withhold information, such as trade secrets and privileged or confidential commercial or financial information (Exemption 4) and personnel, medical, and similar files, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy (Exemption 6). FOIA generally does not *require* nondisclosure of exempt information, but often gives the agency discretion to release exempt information from which foreseeable harm is not likely to result to the agency or the submitter.

It is DOE's objective to disclose to the public the maximum amount of information regarding its mission-related activities, including research involving human subjects, consistent with privacy and national security interests.[3] To the extent permitted by other laws,[4] DOE will disclose, upon request, information that FOIA otherwise would permit to be withheld.

It is DOE's policy, however, to protect the privacy of individuals and not to release personally identifiable human subjects research data in the absence of the subjects' consent or that of surviving family members, or unless pursuant to court order.[5]

The Privacy Act[6]

The Privacy Act of 1974 provides an orderly procedure for managing DOE's systems of records in which information is retrieved by personal identifier.[7] By regulation,[8] DOE can rely on

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[2]5 USC 552.

[3]10 CFR 1004.3(e) (59 Fed. Reg. 63884, Dec. 12, 1994) states that DOE-owned records that are produced by and in the possession of a contractor will be disclosed under FOIA unless they are exempt. This policy applies particularly to records concerning the environment, public health or safety, or employee grievances, but does not apply to privileged information or information having commercial value.

[4]DOE 1700.1, Nov. 19, 1979, section 2.c.

[5]Upon request through appropriate channels, this information can be lawfully released to Congress.

[6]5 USC 552a.

[7]Files of contractors carrying out Federal functions are covered by the Privacy Act as well.

[8]10 CFR 1008.5(b).

Privacy Act conditions of disclosure[9] to withhold information from a person other than the person to whom the record pertains only when the information also is exempt from disclosure under FOIA. The Privacy Act's value, therefore, lies in the access it provides (with exceptions) to DOE records by the individuals to whom the records pertain. The Act also requires that DOE inform individuals of the intended uses to which the data they provide will be put, including any voluntary or mandatory disclosures anticipated, and limits information collected to that relevant and necessary to accomplish specific purposes of the agency. Information in DOE records can be used by DOE employees in their duties, and for this purpose, "DOE employees" include contractors that operate systems of records on behalf of the agency.

Federal Regulation on Protection of Human Subjects

It is DOE's policy that the rights and welfare of human subjects involved in research supported or sanctioned by DOE[10] be protected. The DOE Regulation on Protection of Human Subjects (10 CFR Part 745, the "Common Rule") and DOE Order 1300.3 (August 23, 1990) establish the requirements that implement this policy. Research activities involving human subjects may not be initiated until DOE is satisfied that compliance with the requirements has been achieved, as evidenced by IRB approval of specific projects and protocols. Section 745.111(a) provides that, to approve research covered by the Common Rule, an IRB must determine that, among other requirements, adequate provisions are provided to protect the privacy of subjects and to maintain the confidentiality of data, where appropriate.[11]

Other Laws That Could Affect DOE-Supported Human Subjects Research

Specialized Federal laws applicable to specific situations or unique to certain Federal agencies may affect the management of identifiable human subjects data involved in DOE-supported or controlled research in given situations. For example, specific confidentiality protections are provided for information relating to substance-abuse patient information (Public Health Service Act, section 543) and specific protective statutes for research information apply to the National Center for Health Statistics, the Agency for Health Care Policy and Research, the Census Bureau, and the Departments of Justice and Veterans Affairs.

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[9]5 USC 552a(b).

[10]This policy covers all DOE elements and all contractors and subcontractors performing work for the Department, as provided by law and/or contract, and as implemented by the appropriate contracting officer. It explicitly covers non-DOE funded work performed at DOE-owned, -leased, or -controlled facilities (DOE Order 1300.3., section 2.)

[11]Unless otherwise provided by law, section 745.101(i) permits the Secretary to waive the applicability of some or all of the provisions of the Common Rule to specific research activities or classes of research activities otherwise covered by the Common Rule. In view of DOE's previously stated policy to protect research subjects' privacy, in the absence of their or their survivors' consent or as otherwise ordered by a court of competent jurisdiction, it may be assumed that this authority would be exercised by the Secretary of Energy in only exceptional and limited circumstances, where pressing need can be demonstrated and justified.

State

In addition to protections that may be provided to personally identifiable human subjects research data at the Federal level, certain constraints may also be provided at the respective state levels through statute or legal precedent established by state courts.[12] *With few exceptions, state statutes require the considered, orderly management and use of personally identifiable information and are not absolute bars to its disclosure.* Questions regarding the effect of potentially applicable state restrictions on disclosure of specific human subjects data may be referred to the DOE Office of General Counsel (GC-52) at (202) 586-6975 or Fax (202) 586-6975.

Laws at the state level may explicitly provide for disclosure for use in research, frequently with the requirement for IRB approval. The Model Law (see footnote 12, *supra.*), for example, permits disclosure where an IRB has determined that the research is important enough to warrant intrusion into the subjects' privacy; it would be impracticable to conduct such research without identifiers; reasonable safeguards are provided against redisclosure, and procedures are provided to remove or destroy identifiers at the earliest opportunity, unless retention is approved by the IRB.[13]

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[12]Avenues for restricting disclosure of human subjects data at any particular state level might include—

- Comprehensive statutes that protect the confidentiality of health care information. Approximately a dozen states have such laws; Montana and Washington have enacted the Uniform Health-Care Information Act (the Model Law), developed by the National Conference of Commissioners on Uniform State Laws.
- Statutes that cover specific kinds of health-related information, such as HIV infection/AIDS and mental health data. Some states protect information generated within their state-operated health care facilities.
- State court decisions based on theories of implied contract, invasion of privacy, and malpractice.
- The physician-patient privilege against disclosure in legal proceedings.
- Statutes protecting from disclosure information gathered by certain organizations or for certain uses, such as state health department or vital-statistics records, data held by insurance companies and, less frequently, data collected for use in research.
- Laws protecting Medicaid data from disclosure except for purposes of the Medicaid Program, as required by the Social Security Act [Section 1902(a)(7)].

Statutes in some states explicitly provide for disclosure of data for use in research, usually on condition of Institutional Review Board approval. The Model Law, for example, would permit disclosure where an IRB has determined that the importance of the research outweighs the subjects' rights to privacy; it would be impracticable to conduct the research without identifiers; reasonable safeguards are provided against redisclosure, and procedures are provided to remove or destroy identifiers at the earliest opportunity, unless retention is approved by the IRB. [Model Law, section 2-104(a)(7)]

[13]Section 2-104(a)(7).

Restraints on disclosure at the state level also may include, in applicable situations, testimonial physician-patient privilege; state court decisions based on theories such as implied contract, invasion of privacy, and malpractice; laws protecting information gathered and held by state health departments, insurance companies, in vital records systems, or for research; and laws protecting Medicaid data, as required by the (Federal) Social Security Act.[14]

[14]Section 1902(a)(7).

Cooperative Research

A. Introduction

This chapter stresses the fundamental principle governing cooperative research projects—that each participating institution is responsible, both specifically for safeguarding the rights and welfare of the human subjects involved and generally for compliance with the Common Rule.

> ***Cooperative Research**—Projects involving one or more institutions, each of which is responsible for safeguarding the rights and welfare of human subjects.*

Section B of the chapter offers points to consider when one institution seeks review and approval of human subjects research projects from an institutional review board (IRB) at a second institution. Figure 8a is a Sample Interinstitutional Assurance for arrangements of this sort. The section also suggests possible alternative arrangements, such as a common IRB.

Section C highlights the requirements for cooperative research projects in 10 CFR 745 and outlines types of cooperative arrangements. In addition to the Interinstitutional Assurance discussed in Section B, these include Cooperative Project Assurances (CPAs) for multiprotocol, multisite research under Cooperative Protocol Research Programs (CPRPs) recognized by the Office for Protection from Research Risks (OPRR) within the Department of Health and Human Services (DHHS). Figure 8b is an OPRR Report dated November 9, 1992, entitled "Local IRB Review of Multicenter Clinical Trials."

Section C also outlines types of cooperating institutions, possible and recommended IRB review arrangements, and types of funding mechanisms, from Cooperative Research and Development Agreements (CRADAs) to Work for Others.

B. General Guidance on Cooperative Research Projects

10 CFR 745.114 permits cooperative research projects covered by the Common Rule and involving more than one institution and potentially more than one IRB. With the approval of the U.S. Department of Energy (DOE), an institution participating in a cooperative project may enter into a joint review arrangement, may rely upon the review of another institution's qualified IRB, or may make similar arrangements in order to avoid duplication of efforts. *[See the Sample Single/Multiple Project Assurance (Figure 4a) in Chapter 4 of this handbook.]*

In conducting cooperative research, each participating institution is responsible specifically for safeguarding the rights and welfare of the human subjects involved and generally for compliance with the Common Rule.

In conducting cooperative research, each participating institution is responsible specifically for safeguarding the rights and welfare of the human subjects involved and generally for compliance with the Common Rule. Consequently, a decision to rely upon the judgment of another IRB should be made only after careful consideration of all circumstances surrounding the project by the IRB, the affected institution, and DOE. The following factors should be considered:

- Do the participating institutions draw from culturally dissimilar research subject populations?
- Are the participating institutions located in different states or other geographical subdivisions that have varied and, perhaps, differing legal or regulatory requirements, procedures, and norms?
- At which institution is the human subjects involvement to take place?
- Are the participating institutions accustomed to or familiar with each other's operating policies, constraints, procedures, and commitments? Are there special concerns—for example, does one of the participants question or feel dissatisfied with the other's compliance with regulatory requirements, such as drug control?

Reference Material Included In This Section

- Sample Interinstitutional Assurance (Between Institutions A and B) (Figure 8a).

Other options for resource-saving IRB arrangements for cooperative projects that have been found to comply with the letter of the Common Rule generally include the following:

- Where institutional sites are geographically close, they may contribute membership to a common IRB, sharing in the costs of operation, while providing reviews for protocols and projects that may be used by investigators at some or all of the sites. The common IRB then can be equally cited as the IRB of record by all sites that contribute to its membership.

- Among the IRBs of the participating institutions, an IRB that has unique expertise, a legal or administrative incentive or preference for involvement, or other special qualifying characteristics may host reviews for other nearby institutional sites, with consultant representation from each other site present for all initial and continuing reviews of protocols and projects jointly used by all of the sites.

In its review and approval, DOE will give each case individual consideration as to appropriateness of cooperative IRB arrangements.

Figure 8a. Sample Interinstitutional Assurance (Between Institutions A and B)*

Statement of Principles and Policies for Protection of Human Subjects

Ethical Principles

- Institution A is guided by the ethical principles regarding all research involving humans as subjects as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (known as the "Belmont Report").

Institutional Policy

- Institution A acknowledges and accepts its responsibilities for protecting the rights and welfare of human subjects participating in research activities conducted at or sponsored by this institution.

- Institution A assures that before human subjects are involved in research, proper consideration will be given to—

  - The risks to the subjects.
  - The anticipated benefits to the subjects and others.
  - The importance of the knowledge that may reasonably be expected to result.
  - The informed consent process to be employed.
  - The need for additional safeguards in the case of especially vulnerable subjects.

- Institution B will exercise appropriate administrative overview carried out at least annually to ensure that its practices and procedures designed for the protection of the rights and welfare of human subjects are being effectively applied.

- Institution A will be responsive to institution B with regard to the protection of human subjects and satisfaction of the intent and procedures as specified in 10 CFR 745 and other applicable rules and regulations.

- Institution A will cooperate in compliance with these regulations as though it received funds for its participation in the project directly from DOE or the Department of Health and Human Services (DHHS). For the purpose of this affiliation, compliance will take the form of reliance upon the review of institution B's qualified IRB. This arrangement seeks to avoid the duplication of review effort by both institution A and institution B.

Continued—

* Institution A: Institution relying on another institution's IRB review.
Institution B: Institution with an assurance that covers the research.

Figure 8a. Sample Interinstitutional Assurance (Between Institutions A and B) *(Continued)*

Agreement to Comply with Federal Regulations (10 CFR 745, as amended, "DOE Regulations")

The officials signing below agree that the research activity entitled:
"_____,"
under the direction of _____, at the _____,
will be conducted in accordance with DOE/DHHS policies, procedures, and regulations for the protection of human research subjects (10 CFR 745) as provided for in their applicable institutional assurances and in accordance with the stipulations of the designated DOE/DHHS approved IRB. The _____ has responsibility for certifying future IRB reviews and for reporting to DOE/DHHS as may be required.

Institution Not Conducting a DOE/DHHS-Approved IRB Review

Name and Address: _____

_____

Name of Institutional Official: _____
Title: Chair, [IRB name] _____
[phone number] _____

Signature: _____ Date: _____

Date of approval: _____ None (EXEMPT) _____ Project #: _____

Institution Conducting a DOE/DHHS Approved IRB Review

Name and Address: _____

_____

Name of Institutional Official: _____
Title: Chair, [IRB name] _____
[phone number] _____

Signature: _____ Date: _____

Date of approval: _____
Assurance #: _____ IRB #: _____

DOE or DHHS Approval Official

Signature: _____ Date: _____

Name: _____ Phone: _____
Title: _____
Address: _____

C. Cooperative Research Projects

Legal Requirements: 10 CFR 745 Section 114

Reference Material Included In This Section

- OPRR Reports, 93–01 (Figure 8b).

"Cooperative research projects are those projects covered by this policy which involve more than one institution. In this 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."

The requirements of DOE Order 1300.3 (August 23, 1990) and 10 CFR Part 745 must be met before any DOE-supported or sanctioned research activity involving human subjects begins. Where any part of a cooperative research project, including a CRADA, is to be performed solely by the Partner at the Partner's site, the Partner will determine whether the work involves human subjects research subject to 10 CFR Part 745, as defined in that Part. If so, the Partner will provide its determination, with the results of its IRB review, if applicable, and any other information relevant to this aspect of the project, to DOE, before work is initiated under the applicable agreement.

Types of Cooperative Assurances

Interinstitutional Assurance

An official agency approval document is designed to permit one institution to provide IRB review of cooperative research projects whose terms are binding on the other institution(s). *(For examples, see General Guidance on Cooperative Research Projects in this chapter and Figure 8a.)*

Cooperative Project Assurance

A CPA is an agreement that covers participation in OPRR-recognized CPRPs. CPRPs involve multiprotocol, multisite research in which data from standardized protocols are pooled across institutions. These protocols are approved and monitored by DHHS Protocol Review Committees, which are recognized by OPRR as satisfactorily addressing the adequacy of human subjects protections. Once approved, the CPA is valid for participation in *all* OPRR-recognized CPRPs.

Cooperative Research

In the past, a variety of assurances were used for certain cooperative research projects. Examples include—

- Clinical Community Oncology Program.
- Cooperative Oncology Group Program.
- Community Program for Clinical Research on AIDS.

These are being replaced by CPAs as they expire.

Types of Cooperating Institutions

- Domestic institution with a Multiple Project Assurance (MPA) on file with DOE or OPRR.
- Domestic institution with IRB, but with requirement to submit a Single Project Assurance (SPA) with each new protocol.
- Domestic institution with no IRB.
- Foreign institution.

Types of Cooperative Agreement Funding Mechanisms

Cooperative Research and Development Agreements (CRADAs) Field Work Proposals Interagency Agreements Interlaboratory Transfers Laboratory Directed Research Development Funds Pilot Projects	Program Grants Research Grants Special Research Grants Thesis Research User Facility Agreements Work for Others

IRB Review Options

IRB review may be conducted by any of the following:

- IRB review at each cooperating institution.
- Single IRB of record with members from all cooperating institutions.
- Host IRB with representatives from cooperating institutions. This method is being discouraged in cases where a cooperating institution has a qualified IRB because the policy states that responsibility for protection of human subjects is the responsibility of *each* IRB. This approach allows consideration of such local factors as laws, population diversity, and community standards.
- Use of one qualified IRB to conduct review for all cooperating institutions.

Recommended IRB Review—Domestic Cooperative Agreements

DOE Facility Nature of Assurance	Cooperating Facility Nature of Assurance		
	SPA	MPA	No IRB
SPA	Both Review	Both Review	DOE Review
MPA*	Both Review	Both Review	DOE Review
No IRB	DOE/OPRR Review	DOE/OPRR Review	NA

Options

1. Request DOE approval to use cooperating institution's IRB for review of project.
2. Request agency approval to use either DOE or cooperating institution's IRB for review of project.
3. If either option is used, reviewing IRB must ensure that cooperating institution will comply with reviewing IRB's DOE or OPRR assurance provisions.

*May be granted by either DOE or OPRR.

Figure 8b. OPRR Reports, 93–01

Number 93–01
Human Subject Protections

OPRR Reports

NIH PHS HHS

November 9, 1992

Subject: Local IRB Review of Multicenter Clinical Trials

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) Chairpersons throughout the country. Its purpose is to clarify procedures for local IRB review of National Institutes of Health (NIH) multicenter clinical trial protocols that include NIH-approved sample informed consent documents. These procedures complement the informed consent requirements of Department of Health and Human Services (DHHS) regulations as follows:

(1) The Office for Protection from Research Risks (OPRR) now requires that each local IRB review 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.

(2) 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.

(3) The justification for approval of such deletions or modifications must be reflected in the IRB minutes. For trials sponsored by the National Cancer Institute (NCI), investigators must forward copies of such IRB-approved changes, with their justifications, to the appropriate Cooperative Group headquarters.

This policy should be implemented immediately for the initial local IRB review of any multicenter clinical trial protocol with an NIH-approved sample informed consent document. For trials that are currently in progress, the policy should be implemented at the next scheduled continuing IRB review.

This policy does not reflect any change in OPRR's policy concerning the importance of local IRB review or the local IRB's profound responsibility for protecting human subjects. Only the local IRB is familiar with the particular circumstances of its research setting and is in a position to weigh critical considerations like state and local laws, professional and community standards, institutional policies, and the needs of differing patient or subject populations. Thus, the local IRB is in the best position to ensure that persons deciding whether or not to enroll in research have the greatest level of accurate information necessary to make that decision. Each IRB must continue to review all protocols and informed consent documents with the greatest of care, regardless of any prior review at the national level.

Melody H. Lin, Ph.D.
Acting Director
Division of Human Subject Protections
OPRR

John G. Miller, D.V.M.
Acting Director
OPRR

NINE

International Research

Introduction

It is important that all research with human subjects adequately protects the rights and welfare of the subjects. All human subjects research funded by the U.S. Government that would be subject to the Federal regulations if it were conducted wholly within the United States must comply with the Federal regulations for the protection of human subjects in all material respects.

Title 10 CFR Part 745 has a special provision for international research:

> 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 . . . . 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.

Reference Materials Included In This Chapter

- Observations on the Negotiation of Single Project Assurance With Institutions in Foreign Countries (Figure 9a).
- DHHS Documents Related to International Collaborations (Figure 9b).
  - Background Information for U.S. Government Department and Agency Personnel: Protection of Human Subjects in Studies Conducted Outside the United States [Figure 9b(1)].
  - For United States Department and Agency Staff Use: Points to Consider, Protection of Human Subjects, International Research [Figure 9b(2)].
  - Narrative Format for Providing an Assurance for International Research [Figure 9b(3)].
  - Sample Assurance of Protection of Human Subjects in International Research [Figure 9b(4)].

IRB Considerations[1]

The regulations recognize that "the procedures normally followed in the foreign countries [in which the research will take place] may differ from those set forth in this policy" (10 CFR 745). Research may be approved, therefore, if "the procedures prescribed by the foreign institution afford protections that are *at least equivalent* to those provided in this policy." The foreign country's procedures may then be substituted for the procedures required by the Federal regulations. Approval of the substitution is to be given by the relevant Federal department or agency head after review of the foreign procedures; notice of actions taken on such reviews are

[1]OPRR *1993 Protecting Human Subjects Institutional Review Board Guidebook*, p. 6-56.

to be published in the *Federal Register* (or elsewhere, as provided for in department or agency procedures).

The procedure for approving the U.S. Department of Energy (DOE)-supported research with a foreign component begins with the domestic institution with which the U.S. investigators are affiliated. If the U.S. institution has an approved Multiple Project Assurance (MPA) on file with DOE or the Department of Health and Human Services (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. Each foreign institution should, upon request, submit an appropriate assurance to the funding agency. *(Because, at the present time, no international code prescribes exactly the same procedures for protecting human subjects as do the U.S. regulations, the funding agency reviews the actual procedures detailed by the foreign institution as the primary basis for negotiating acceptable assurances.)* International codes will, however, be taken into consideration in the negotiations. If the institution's practices are not equivalent to the U.S. regulations, the funding agency can require that particular procedures be followed before recommending approval of the substitution.

One difficult issue is determining what constitutes "protections that are at least equivalent" to the Federal regulations. In the case of DOE, this determination is made by DOE headquarters (ER-70) Office of Health and Environmental Research (OHER), in consultation with the Office for Protection from Research Risks (OPRR). The broad policy outlines of international standards, such as the Declaration of Helsinki or the Nuremberg Code, are a starting place, but are not alone sufficient. Written descriptions of the specific procedural implementation of such policies that have been adopted by the foreign institution are required. It is important to emphasize that the assurance is with the foreign institution, not with the country.

Recommended IRB Review—International Agreements

DOE Facility Nature of Assurance	Collaborating Facility	
	With IRB	Without IRB
SPA	Both Review	DOE Review
MPA*	Both Review	DOE/OPRR Review

Requirements

1. In any instance of international agreements, document that SPA negotiations have been conducted that determine that provisions are at least comprehensive as the Common Rule.

2. One may request DOE's OHER or OPRR to assist in making a determination of the adequacy of foreign institution's provisions for protection of human research subjects.

*May be granted by either DOE or OPRR.

International Research Considerations

Suggestions

- Seek out countries whose human research regulations are the same as or similar to those established in the United States. The Declaration of Helsinki or the Nuremberg Code may be used as common ground on which to build additional requirements or guidelines. *(Reprints of these documents can be found in the Appendix of this handbook.)*

- Make accommodations for language differences. All project information, including the results of the study, should be made available in the language of the host country. It is beneficial to have the translated material translated back into English to verify accuracy of the original translation. This practice will lessen the likelihood of confusion or conflicts stemming from miscommunication.

- Be aware that research agreement efforts are not efforts to impose American culture or ideas on the host country. The host country should be able to define what is acceptable and appropriate for its country.

- Have a clear understanding of what the host government expects to gain or how it expects to benefit by the research. For example, conflicts have arisen when foreign subjects and researchers were not given access to the results or products of the research performed in their country.

- Be sensitive to cultural nuances and values of the host country and of the community where the research will actually be performed.

- Build on the experience gained by other U.S. researchers who have conducted research in the country where you desire to do research.

Cautions

- International human subjects research agreements can take 1 year or longer to negotiate.

- Some representatives of foreign countries may be willing to sign agreements on the protection of human subjects without knowing with certainty whether the requirements will be accepted and enforced in their country. Make sure the agreement goes through the proper authorities—those persons who have the power to uphold the standards and requirements established in the agreement. Some countries will not give an IRB full power, which may inhibit its oversight and regulatory capabilities.

Additional issues and problems related to negotiations with foreign institutions are discussed in Figure 9a. DOE recommends that institutions conducting DOE-funded research in foreign countries take into consideration the OPRR observations in Figure 9a.

Figures 9b(1)–(4) are sample documents related to international collaborations. These documents were prepared by OPRR and are useful resources in the coordination of international collaborations.

Another useful resource on this topic is the *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects* and *Biomedical Ethics in U.S. Public Policy—Background Paper. (See Chapter 17, Additional References, for more information on these publications.)*

Figure 9a. Observations on the Negotiation of Single Project Assurance With Institutions in Foreign Countries

Provided by:
Dr. T. Puglisi, OPRR, NIH

Observations on the Negotiation of Single Project Assurance With Institutions in Foreign Countries

October 24, 1991

- The Assurance must ensure human subject protections that are equivalent to those required domestically. DHHS cannot support research in other countries that would not be acceptable in the U.S. Most foreign institutions appreciate the importance of this principle once it is explained and are often grateful for the guidance that OPRR provides.
- Foreign institutions sometimes question the requirement that they adhere to U.S. regulations since the research is not being conducted within the U.S. OPRR explains that because the research is supported by DHHS, DHHS must ensure that the same standard of protections is afforded to all human subjects, regardless of where the research is conducted. Most institutions provide an acceptable Assurance once they understand why it is required and what needs to be included.
- The Assurance must include a statement of ethical principles governing the institution in the protection of human research subjects. Most domestic institutions rely on the Belmont Report. Foreign institutions rely on other codes (e.g., the Helsinki Declaration).
- Common areas of misunderstanding (addressing these issues "up front" often saves time and helps prevent misunderstanding):
  - IRB Membership: Many institutions fail to include a nonaffiliated member, a female member, or a nonscientist until reminded. Where medical protocols are involved, OPRR usually requires that two physicians be included as well.
  - Conflict of Interest: This concept may not be well understood in certain cultures. It is sometimes necessary to explain that the regulations prohibit investigators from participating in the IRB review of their own projects (except to provide information).
  - Definition of Human Subjects: The regulatory definition of "human subjects" is very broad. Some researchers are surprised that their activities constitute "research involving human subjects."
  - Informed Consent Documents: Many institutions fail to understand the need for a written informed consent document or fail initially to develop a fully satisfactory document. This often requires some explanation and negotiation.
  - Signed Documentation of Informed Consent: Many institutions fail to understand the need for signed documentation of informed consent. This may also require some explanation and negotiation. Note that it may be acceptable for the IRB to waive signed documentation under Section 117(c). This requires a specific waiver by the IRB with appropriate justification.
  - Expedited Review: OPRR does not permit expedited review under Single Project Assurances [authority at Section 110(d)].

Figure 9b. DHHS Documents Related to International Collaborations

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

December 3, 1992

FROM: Acting Chairman, Human Subjects Research Subcommittee

SUBJECT: Transmittal of Documents Related to International Collaborations

TO: Members, Human Subjects Research Subcommittee
Committee on Life Sciences and Health

The Working Group on International Issues of the Human Subjects Research Subcommittee has prepared the enclosed documents which have been reviewed by the entire Subcommittee. These are for you to distribute to the appropriate personnel within your Department or Agency for their use in implementing the Common Rule for research involving human subjects conducted or supported by the Federal Departments or Agencies.

The "Background Information for U.S. Government Department and Agency Personnel, Protection of Human Subjects in Studies Conducted Outside the United States" and the "Points to Consider, Protection of Human Subjects, International Research" documents are intended primarily for use by Federal personnel.

The "Assurance of Protection for Human Subjects in International Research" document and the "Narrative Format for Providing an Assurance for International Research" may be distributed to Foreign Collaborators.

The Working Group and Subcommittee documents represent considerable effort to develop a workable approach to application of the Common Rule in international settings, and I am sure these will be most useful to you in implementing the Rule.

Please contact Dr. Joan P. Porter at (301) 496-7005 if you need additional information.

John G. Miller, D.V.M.
Acting Director
Office for Protection from Research Risks
National Institutes of Health

Enclosures

Figure 9b(1). Background Information for U.S. Government Department and Agency Personnel: Protection of Human Subjects in Studies Conducted Outside the United States

This information package is provided to guide U.S. Government personnel who design, review or carry out research involving human subjects in foreign settings. The purpose of these materials is to inform the reviewing U.S. Government officials of the responsibilities of Departments and Agencies. These Departments and Agencies must adhere to the requirements of U.S. law and Federal regulations governing the protection of human subjects involved in research conducted, supported or otherwise subject to regulation by the Federal Government outside the U.S. The Common Rule (Federal Policy for the Protection of Human Subjects—copy enclosed *[see Chapter 2 of this handbook]*) states that any research involving human subjects, supported or conducted in whole or in part by Federal Departments or Agencies, in either foreign or domestic settings, is subject to the Common Rule.[7] In the event that research does not meet the standards of the Common Rule, the Department or Agency must either (1) assure that any deficiency is corrected, [or] (2) obtain a waiver from the official designated by the Common Rule as authorized to grant waiver. Unless the Common Rule standards can be met, Federal Departments and Agencies will not be able to participate in the research.

Procedures normally followed in foreign countries to protect human subjects may differ from those in the Common Rule. If a Department or Agency Head or designee determines that the procedures prescribed by the foreign institution afford protections that are "at least equivalent" to those in the Common Rule, the Department or Agency Head may approve the substitution of the foreign procedures in lieu of those in the Common Rule.

Several international declarations have been formulated to address the involvement of human subjects in research. These are often cited in reference material submitted by foreign institutions and are provided for your information in this chapter. The first attempt to set international standards was the Nuremberg Code of 1947. This was an outgrowth of the Nuremberg Trials of war criminals who performed experiments on prisoners and detainees during the Second World War. The Nuremberg Code was followed in 1964 by the Declaration of Helsinki, which was itself revised several times by the World Medical Assembly. The most recent internationally recognized document is the Proposed International Guidelines for Biomedical Research Involving Human Subjects, which was produced in 1982 as a joint project of the World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS). This document is currently under revision. Another important historical document in the U.S. is the Belmont Report—Ethical Principles and Guidelines for the Protection of Human Subjects of Research, produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. *[The Belmont Report is included in the Appendix of this*

[7]Food and Drug Administration (FDA) Regulated Research: Foreign clinical studies conducted under an FDA research permit [Investigational New Drug Exemption (IND) or Investigational Device Exemption (IDE)] must be reviewed by an Institutional Review Board which meets the organizational and functional requirements specified under 21 CFR Part 56. The FDA may accept studies not conducted under a research permit provided that the studies are well designed, well conducted, performed by qualified investigators, and conducted in accordance with the ethical principles contained in the "Declaration of Helsinki," or the laws and regulations of the country in which the research was conducted, whichever represents the greater level of protection for the research subject. (21 CFR 312.120) See "Points to Consider" document page 4, item H, enclosed* or consult Mr. Richard Klein, FDA, 301-443-1382.

Continued—

* Not included.

Figure 9b(1). Background Information for U.S. Government Department and Agency Personnel: Protection of Human Subjects in Studies Conducted Outside the United States *(continued)*

handbook]. Each of these documents contains many laudable policies and principles, and are commendable efforts in the evolution of the concept of human subjects protections. It is important to note, however, that while some international codes contain laudable policies and principles, including ethical review by an appropriate review committee, informed consent and meaningful risk/benefit assessment, none to date lays out well a mechanism to implement them. Accordingly, a mechanism needs to be found to supplement international codes to implement these essential principles. It is necessary, therefore, to begin negotiations with foreign collaborators to supplement international codes to meet requirements of the Common Rule. Careful review is necessary to make certain that procedural requirements under the Common Rule are met and research can go forward.

The enclosed "Points to Consider" provide a framework in which appropriate evaluation of research proposals submitted by foreign governments and institutions can be accomplished. The Common Rule requires that entities that receive Federal support to conduct research involving human subjects provide an Assurance document that specifies how the provisions of the Common Rule will be implemented. Enclosed is a sample "Assurance of Protection for Human Subjects in International Research" as a model document for foreign governments or institutions involved in research supported by the Department or Agency. This document contains all the essential elements required by the Common Rule and can be used as written to assure acceptable procedures. Many institutions will choose to base their Assurance on this sample document; however, should the institution prefer to develop its own Assurance document, the sample document may be used for a point by point comparison with the locally developed document to determine the areas needing further discussion, negotiation, revision, or exemption. Also enclosed is a "Narrative Format" that alternatively could be used as the basis for preparing an assurance document.

It is important to recognize that the requirements of the Common Rule are *minimum standards.* The issue of protection of human subjects is one that cannot be entirely categorized and addressed by regulations. The principles set down by the policy must be taken into consideration in light of the culture and best interests of the subject. While exemption from certain requirements of the Common Rule may decrease the cost, difficulty, political or social complexity of performing a study, these considerations do not offer sufficient justification to waive protections afforded the subject.

Although it will be the rare exception, circumstances may exist wherein the best interests of the subject are served by waiver of one or more of the requirements of the Common Rule. Procedures for granting such a waiver must be established by each Department or Agency adopting the Common Rule. The Working Group on International Issues of the Human Subjects Research Subcommittee of the Committee on Life Sciences and Health, Federal Coordinating Council on Science Engineering and Technology, is available to Departments and Agencies to provide consultation concerning the waiver and other interpretation of Federal law and regulation in the area of protections of human subjects. The Working Group will offer recommendations to responsible officials regarding any issues or questions that arise in this evolving and complex area. It is important to note that the recommendations of the Working Group are advisory in nature and neither limit nor usurp the authority or responsibility of Department or Agency officials as designated in the Common Rule. Contact the Human Subjects Research Subcommittee Member, _____ to initiate this process.
Name and Number

Figure 9b(2). For United States Department and Agency Staff Use: Points to Consider, Protection of Human Subjects, International Research

A. Are Human Subjects *Involved*?

1. Does the proposed research provide a detailed description of the involvement of human subjects? What are the characteristics of the subject population, including the anticipated age range and health status? What is the gender and racial/ethnic composition? Are fetuses, pregnant women, children, prisoners, institutionalized or other vulnerable persons involved?
2. Are data about living, identifiable individuals involved in the form of specimens, records, or other data? [See Sec.102(f) Common Rule]
3. What are the potential physical, psychological, social, legal, or other risks? What is the likelihood of these risks occurring?
4. Are there alternative treatments?
5. What procedures are there to minimize risks, including loss of confidentiality? What kind of medical or professional interaction is available in the case of adverse effects to subjects? Are there methods to monitor data collected to ensure safety of participants?
6. Are the risks to subjects reasonable in relation to anticipated benefits to subjects and to knowledge expected to result from the research?

B. Is the Research *Exempt*? See the exempt categories in Sec.101(b)1-6 of the Common Rule.

C. Institutional Review Board (IRB)

1. Is there a domestic institutional review board that will review the research?

   and/or

   Is there a local group that can meet the criteria and perform the functions of an institutional review board? If so, where is it located?

2. Who are the members? Can the membership criteria in Sec.107 of the Common Rule be fulfilled?
3. Are there any conflicts of interest? E.g., the investigator(s) must not be a member [of the IRB] for purposes of his/her research, vote, or be present during IRB proceedings [the review of his/her project] except to present his/her research and to answer questions. Family members of the investigator(s) must not be members [of the IRB], and so on.
4. Does/will the IRB assess—
   - Risks to subjects and how they can be minimized?
   - Risk/benefit ratio?
   - Equitable selection of subjects?
   - Informed consent process, context, and documentation?

Continued—

Figure 9b(2). For United States Department and Agency Staff Use: Points to Consider, Protection of Human Subjects, International Research *(continued)*

- Confidentiality?
- Special protections for vulnerable subjects?

5. Does/will the board meet as often as needed and at least annually?
6. Does/will the board keep minutes and records? [Sec.115]
7. Does the board have sufficient autonomy and authority to be able to disapprove a protocol or to take action to suspend or terminate a protocol? [Sec.113]

D. Reporting [Sec.103(b)(5)]

1. How will the research institution report to the Department or Agency (and to the IRB) unanticipated problems involving risks to human subjects, instances of serious noncompliance or suspension or termination of IRB approval?

E. Informed Consent

1. What is the process to inform subjects about the study?
2. Are all the elements of informed consent included in the process? [Sec.116(a)] If not, why not?
3. Is there any exculpatory language? [Sec.116]
4. Will a short form or long form be used? [Sec.117(a)(b)]
5. Where will documents be kept (if applicable)?
6. Is there a provision to give each participant an informed consent document (if applicable)? [Sec.117(c)]
7. If informed consent or parts of it are waived, can this be justified? I.e., is the study minimal risk? *and* will waiver or alteration affect the rights and/or welfare of the subjects? *and* could the research not be practicably carried out without alteration or waiver? *and*, if appropriate, will subjects be provided with additional information after the study? [Sec.116(d)] Note that clinical research involving FDA-regulated products must meet the requirements of 21 CFR Part 50, which does not include a waiver provision for informed consent.

F. Documentation

Does/will the institution provide accurate documentation addressing the following?

1. A statement of principles governing protection of human subjects in the institution in protecting human subjects? [Sec.103(b)(1)]
2. The institutional review board and its membership? [Sec.103(b)(3)]
3. The procedures it will follow to conduct initial and continuing review and report findings and noncompliance, and review changes to the protocol? [Sec.103(b)(4)&(5)]
4. The name of the responsible official who will act for the institution in protecting human subjects?

Continued—

Figure 9b(2). For United States Department and Agency Staff Use: Points to Consider, Protection of Human Subjects, International Research *(continued)*

G. Additional Considerations—Based on Experience in Implementation

1. It is important to emphasize that human subjects protections are important during the initial formulation of research. Participants need to be aware that there are requirements for descriptions, analysis, review, and documentation.
2. Situations which result in conflicts of interests on an IRB often arise when institutions assemble an IRB with the investigator(s) as a member. In addition, if the IRB is the same group that formulates and endorses the scientific approach for the proposed research, there is an inherent conflict of interest. This type of situation should be discussed during initial discussions with foreign collaborators.
3. Informed consent procedures do allow some flexibility in documentation and information given, but justifications for flexibility must be carefully delineated.
4. Permission from community and/or tribal leaders may be necessary for the success of the project, but it must not substitute for individual informed consent. Waiver of individual consent may be made if conditions in Sec.116 are met and approved by the IRB.

H. Food and Drug Administration—Regulated Products

Does the research involve an FDA-regulated product (drug, biologic, device, food additive or color, radiation-emitting device)?

1. Is the research covered by an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)?

   If so, the FDA informed consent and IRB requirements (21 CFR 50 and 21 CFR 56) must be met. Please note that the FDA regulations do not provide for exempt categories of research.

2. If the research is not covered by an IND, is the research being conducted in accordance with ethical principles of protecting the rights and welfare of the subject, that either meet or surpass the standards of the Declaration of Helsinki, amended 1989? (If the ethical standards of the country in which the research was conducted are used, the applicant must state in detail any differences between the standards and the Declaration of Helsinki and explain why they offer greater protection to the human subjects.) [21 CFR Part 312.20] [21 CFR Part 814.14.]

Figure 9b(3). Narrative Format for Providing an Assurance for International Research

1. Please describe what *principles* govern your institution that address protecting the rights and welfare of human subjects of research (e.g., Declaration of Helsinki, Council of International Organizations of Medical Sciences Proposed Guidelines).

2. Please describe the institutional review board (IRB—group to protect human subjects) in your institution which can act to review this protocol to protect human subjects. The IRB must be able to address the following concerns: minimizing risks to participants; risks to participants and benefits to participants and others; fair selection of participants; special protections for vulnerable participants; informed consent of participants and how this will be documented; monitoring data for safety; confidentiality of data.

3. Please describe the *membership* of the IRB. Who serves as chairperson? Who are the members? What are their educational degrees and affiliations? (The IRB should include at least five persons; at least one unaffiliated with the institution; one scientist; one non-scientist; both men and women; someone with expertise about the research and someone who knows about the community(ies) from which participants will be drawn.) Note that the principal investigator or family members will not be part of the IRB proceeding or vote.

4. Please describe how the IRB will conduct its initial and continuing review and how the IRB will be informed promptly of any changes contemplated in the protocol.

5. Please describe the *informed consent process* and provide the document(s) to be used to advise participants about the research and seek their consent. [List items from Sec.116]

   If informed consent is not obtained via a written document, please describe how the consent will be obtained. There must be a witness to the oral presentation to sign the document containing the information presented to the participant.

   If informed consent is not sought or all the elements are not addressed, please indicate the conditions that the IRB cites that are appropriate to justify waiving as described in Sec.116.

6. Please describe how you will maintain the *records* (copies of research protocols; minutes; review records; correspondence; IRB membership, with degrees and affiliations; procedures; statements of new findings to give to participants).

7. Please describe how the IRB, your institution, and this Department will be *informed* of any serious or continuing noncompliance with human subjects protections or if the IRB has suspended or withdrawn its approval.

8. Please provide the *signature* of the institutional official responsible for this project and for making sure that human subjects are protected.

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research

(NAME OF INSTITUTION)

(Name of Institution), hereinafter known as the "institution," hereby gives assurance that it will comply with the principles and procedures for protecting human research subjects specified below.

PART 1
Ethical Principles and Institutional Policies Governing Research Involving Human Subjects

I. Ethical Principles Governing Human Subjects Research

This institution is guided by the ethical principles regarding research involving human subjects set forth in the ___***___. These ethical principles guide the institution in the conduct of all its human subjects research.

*** NOTE In Section I above, the institution may choose to cite *the Belmont Report, the Declaration of Helsinki*, or another appropriate code, declaration, or statement of principles that is consistent with the terms of this Assurance.

II. Institutional Policies Governing Human Subjects Research

A. This institution acknowledges and accepts its responsibilities for protecting the rights and welfare of all human subjects involved in the research that it sponsors or conducts.

B. This institution encourages and promotes an institutional atmosphere that safeguards the rights and welfare of human subjects.

C. It is the policy of this institution that before human subjects are involved in research that it sponsors or conducts, proper consideration must be given to—

(1) The risks to the subjects.
(2) The anticipated benefits to the subjects and others.
(3) The importance of the knowledge that may reasonably be expected to result.
(4) The informed consent process to be employed.

D. Whenever appropriate, it is the policy of this institution to consider special safeguards for protecting research subjects who may be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

Continued—

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

PART 2
Human Subject Protections for Research
Supported by the United States Government

I. Applicability

Part 2 of this Assurance applies only to the following research project that is conducted or sponsored by this institution and supported by the United States Government:

Project title: _____

Project number: _____

Project Investigator/Director: _____

II. Institutional Responsibilities

A. This institution recognizes that all human subjects research supported by the United States Government, including the project referenced above, must be conducted in accordance with the United States Federal Policy for the Protection of Human Research Subjects.

B. The institutional review board (IRB) listed in Attachment A has been designated to be responsible for the initial and continuing review of the project referenced above. The IRB includes at least five persons, including at least one scientist, one nonscientist, and one person not otherwise affiliated with the institution. Every nondiscriminatory effort has been made to include both women and men. The IRB also includes persons who are sensitive to the concerns of the populations from which subjects will be recruited.

C. Provisions have been made to provide both meeting space for the IRB and sufficient staff to support the IRB's review and record keeping duties.

III. IRB Responsibilities

A. The project referenced above has been and will be reviewed at convened meetings at which a majority of IRB members are present. A majority vote of those members present at the meeting is required for approval. The research investigators and their family members may not participate in IRB proceedings except to provide information requested by the IRB.

B. The IRB used the following criteria to determine that protections for human research subjects in this project are adequate:

(1) Risks to subjects are minimized.

(2) Risks to subjects are reasonable in relation to anticipated benefits.

(3) Selection of subjects is equitable.

Continued—

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

(4) When appropriate, the data collected will be monitored during the course of the study to ensure safety of subjects.

(5) Privacy of subjects and confidentiality of data are protected.

C. The IRB has determined that legally effective informed consent will be obtained under circumstances that provide sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. Copies of all informed consent documents for this project are provided at Attachment B.

D. The IRB will review, and have the authority to approve, require modification in, or disapprove project changes.

E. Continuing reviews by the IRB will be conducted at intervals appropriate to the degree of risk, but not less than once per year. The IRB may be called into an interim review session by the Chairperson at the request of any IRB member or Institutional Official to consider any matter concerned with the rights and welfare of any subject.

F. The IRB will maintain documentation of its activities to include copies of research protocols, minutes of IRB meetings and continuing review records, correspondence with investigators, IRB membership with degrees and affiliations, IRB operating procedures, and statements of new findings provided to subjects. This documentation will be retained for at least three years after the completion of the project and will be accessible for inspection and copying by the supporting United States Government Agency.

G. The IRB will report promptly to appropriate institutional officials and to the supporting United States Government Agency—

(1) Any unanticipated problems or injuries involving risks to subjects or others.

(2) Any serious or continuing noncompliance with this Assurance or with the requirements or determinations of the IRB.

(3) Any changes in this project which are reviewed and approved by the IRB.

(4) Any suspension or termination of IRB approval.

IV. Responsibilities of Project Investigators/Directors

A. Project investigators/directors accept their responsibility to comply with the stipulations of the IRB and with the terms of this Assurance.

B. Project investigators/directors will report promptly to the IRB proposed changes in this project, and changes will not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subjects.

C. Project investigators/directors will report promptly to the IRB any unanticipated problems or injuries involving risks to subjects or others.

Continued—

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

PART 3
Institutional Endorsement and Certification

Project title: _____

Project number: _____

Project Investigator/Director: _____

Date of IRB approval: _____

The officials signing below assure that the project referenced above was approved by the IRB on the date indicated and that the project will be conducted in accordance with all provisions of this Assurance and of the United States Federal Policy for the Protection of Human Research Subjects.

I. Authorized Official of the Institution Providing This Assurance

Signature: _____ Date: _____

Name: _____
Title: _____
Address: _____

Telephone: _____

II. Authorized Official of the Institution with the IRB
(Include *only* if *different* from the institution above)

This institution authorizes the designation of its IRB for review of the project referenced in this Assurance.

Signature: _____ Date: _____

Name: _____
Title: _____
Address: _____

Telephone: _____

III. IRB Chairperson

Signature: _____ Date: _____

Name: _____
Title: _____
Address: _____

Telephone: _____

Continued—

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

PART 4
Agency Approval

Project title: _____

Project number: _____

Project Investigator/Director: _____

Date of IRB approval: _____

All parts of this Assurance are in compliance with the requirements of the Federal Policy for the Protection of Human Research Subjects.

Agency Approving Official

Signature: _____ Date: _____

Title: _____
Name: _____
Address: _____

Telephone: _____

ASSURANCE NUMBER:

[NOTE: The period for which this document is approved should be defined in accordance with each Department's or Agency's policies.]

Continued—

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

Attachment A
(Please Resubmit as Changes Occur)

DATE: _____

Institutional Review Board (IRB) Membership

Institution providing this Assurance _____

Institution with the IRB (if different from above) _____

Member Name First M.I. Last	Highest Degrees Earned	Primary Scientific or Nonscientific Specialty	Affiliation with Institution(s) Above (Yes/No; If Yes, state which one)	Address and Phone Number for Chairperson Only
*				
**				
NV				

* Denotes chairperson
** Denotes alternates (If any, denote for whom alternate will serve.)
NV denotes non-voting members

Figure 9b(4). Sample Assurance of Protection of Human Subjects in International Research *(continued)*

Attachment B

Informed Consent Document(s)

Attached copies of all IRB-approved Informed Consent Documents to be used in the project referenced in the Assurance.

Guidance on Occupational, Clinical, and Other Studies

A. Introduction

This chapter first discusses, in Section B, the difference between occupational health surveillance and research. Occupational health surveillance does not constitute research under the terms of 10 CFR 745, but when routine health surveillance gives rise to analytic investigations, those studies do require institutional review board (IRB) review. *In all these cases, it is the IRB that must determine whether or not its review and approval is required, and the IRB must make this determination based on the degree of risk involved in the activity in question.*

Section C deals with the controversial topic of emergency/critical care. It defines emergency care and differentiates it from "compassionate use," a term not used in the Common Rule or in current Department of Health and Human Services (DHHS) or Food and Drug Administration (FDA) regulations. The section notes that DHHS insists on prior IRB approval of research care/treatment; physicians who provide their patients with emergency care may not consider these patients as research subjects or include the outcome of these cases in research reports. Figure 10a presents OPRR Reports 91-01, which articulates and clarifies this DHHS policy. The section also summarizes FDA policies that waive the requirement for prior IRB approval in certain cases and concludes with Figure 10b, FDA's policy statement entitled "Emergency Use of an Investigational Drug."

In some instances, both FDA and DHHS have jurisdiction over the nature and extent of care provided in critical care situations. In these circumstances, the IRB must satisfy both sets of regulations.

Section D summarizes the actions required in case an adverse event occurs. It defines an adverse event and gives examples, discusses reporting it to the IRB, emphasizes the need for prompt treatment of any injury, and outlines questions the IRB should consider and actions it should take, including reporting the event to the Department of Energy (DOE) and others.

When a project is given to the IRB for review and when it is presented to potential participants, all known risks are disclosed. Not all risks can be foreseen, however, and in Section E, the chapter addresses how to handle unforeseen risks, both at the outset (during the informed consent process) and later, if an unforeseen risk becomes evident.

Section F notes that regulations do not determine how human subjects must be compensated for research-related injuries or even whether they should be compensated. The section suggests factors for an institution to consider in deciding whether to offer compensation and, if so, the extent of the compensation. The section concludes with samples of statements that give human subjects information about compensation.

Section G discusses the types of research that *may* not require institutional review board (IRB) review. Management surveys, for example, do not qualify as "research" if the data are not personally identifiable and the intent is to improve an organization's operational effectiveness. By contrast, theses for master's or doctoral degrees do require IRB review if they receive institutional support—for example, use of materials and facilities.

B. Occupational Health Surveillance as Opposed to Research

Occupational health surveillance is the routine monitoring, followup, and assessment for apparent departures from typical health status of U.S. Department of Energy (DOE) and DOE-contractor workers.

Definition

Routine health surveillance involves the standardized, ongoing collection of limited data pertaining to each worker's occupational exposures, demographic characteristics such as age and gender, 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.

A candidate episode is a greater than expected occurrence of health events characterized by a common diagnosis and having at least one other factor in common, e.g., all events occurred among one occupational group, or all events occurred among workers in one laboratory.

Intent

The intent of the occupational health surveillance activities defined above is to protect the health of workers through risk identification. The identification of increases in health risk among workers involves the clarification of which workers are at risk and the determination of whether workplace exposures are associated with increased risk.

Risk/Hazard Assessment

Routine, baseline health surveillance can identify apparent increases in the risk of disease, injury, etc., in workers, but it cannot necessarily link the health event in question with potentially associated occupational exposures. Possible links between unusual health events and occupational exposures can be analyzed through candidate episode assessments, which use well-established data collection techniques to collect additional, more detailed data. Candidate episode investigations are quick-response descriptive assessments conducted to identify potential occupational factors that may be related to the apparent increase in the occurrence of disease, injury, or other health effect. These descriptive assessments use data available on site pertaining to industrial hygiene, occupational medicine, and other relevant health and safety data. Their purpose is to add detail to the data that suggests an apparent increase in the occurrence of the health events of interest.

Need for an IRB Review

The activities discussed above are operational activities consistent with the comprehensive occupational health program of DOE. It is the policy of the DOE Office of Health Studies that routine health surveillance and quick-response candidate episode investigations are a part of the Office's operational occupational health activities. Health surveillance activities as described

above do not constitute research as it is defined in 10 CFR 745; therefore, formal IRB review is not required. However, one should always be mindful of Privacy Act considerations (protection of individual identity), whether the study is funded by sources other than DOE or whether the study will provide results which can be considered to enhance generalizable knowledge (this is research). Every study must be considered on a case by case basis. Therefore, it is recommended that the relevant IRB committees be made cognizant of these activities as part of the process of information dissemination.

When health surveillance indicates the need for an analytic investigation of one or more potential risk factors for the health event under investigation, there is a need for a formal IRB review. These analytic studies will also require coordination between the DOE Office of Environment, Safety and Health (EH-1) and DHHS, through DOE's Memorandum of Understanding with that Agency concerning the conduct of research projects.

There are many gray areas in this arena. When in doubt, investigators should contact DOE's Office of Environment, Safety and Health (EH) or the Office of Health and Environmental Research (OHER) for guidance, *(see Chapter 14, Informational Contacts)*, or submit the project to the IRB for full review and approval.

C. Emergency/Critical Medical Care

10 CFR Part 745.116(f) states, "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."

Reference Materials Included In This Section

- OPRR Reports, 91–01 (Figure 10a).
- U.S. Food and Drug Administration, Emergency Use of an Investigational Drug (Figure 10b).

Regulation 21 CFR 56.102(d) defines emergency care as medical care provided 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. The investigator is still required to obtain informed consent under these circumstances.[1]

The term "compassionate use" should not be confused with the term "emergency care." In the past, the term "compassionate use" was used to refer to the use of investigational drugs outside of an ongoing clinical trial on a limited number of patients who were desperately ill and for whom no standard alternative therapies were available. Currently, the term "compassionate use" does not appear in either FDA or DHHS regulations nor it is referred to in the Common Rule.

The DHHS regulations require that all research care/treatment must have prior approval by the local IRB except where expedited review is specifically permitted [45 CFR 46.103(b)]: Physicians do retain the authority to provide emergency care to their patients. However, the patient may not be considered to be a research subject. The emergency care provided may not be claimed as research and the outcome of such care may not be included in any report of research activity.

The FDA regulations (21 CFR 56.104) regarding emergency care (as defined above) permits the waiver of IRB approval for specific research activities or for classes of research activities. This exemption for the emergency use of a test article is permitted provided the use is reported to the IRB within 5 working days of its occurrence. The IRB is required to examine each case to assure itself that the emergency use was justified. This regulation is intended to be restricted to a single use on one patient by one physician; however, its intention is not to withhold emergency care to a second patient for the purpose of obtaining IRB approval.

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[1] NOTE: As this handbook went to press, the FDA had proposed to amend its current informed consent regulations to permit harmonization of Federal policies on emergency research, and to reduce confusion as to when such research can proceed without obtaining informed consent. The regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject prior to initiation of an experimental treatment. The exception would apply to a limited class of research activities involving human subjects who, because of their life-threatening medical condition and the unavailability of legally authorized persons to represent them, are in need of emergency medical intervention and cannot provide legally effective informed consent. FDA is proposing this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized. Written comments to the proposed rule were due November 6, 1995. As this handbook went to press, the final rule had not been promulgated. *The proposed rule which appeared in the September 21, 1995, Federal Register can be found in the Appendix of this handbook.*

In 1987, FDA established new procedures, "Treatment Investigational New Drug Exemption (Treatment IND)," under which promising new investigational drugs may be made available to patients with life-threatening or serious diseases for which there is no satisfactory alternative drug or other therapies. According to DHHS regulations, Treatment IND must be approved by the local IRB; however, FDA will permit a waiver if the waiver is in the best interest of the subject and adequate alternative mechanisms for human subjects protection are provided (such as national review body).

The IRB must satisfy both FDA and DHHS regulations in cases where FDA and DHHS have jurisdiction over the nature and extent of care provided in critical care situations.

FDA also has a mechanism, "Single Patient Use," that permits the use of an investigational drug for treatment outside of a controlled study. This is usually sought for a single patient who is in a *desperate situation and unresponsive to other therapies* or in a situation where no approved or generally recognized treatment is available. In addition, FDA policy permits IND use when there is little evidence that the investigational treatment is useful but may be plausible on theoretical grounds or anecdotes of success. As with Investigational INDs, DHHS regulations require IRB approval while FDA would permit waivers.

FDA has also recently (*Federal Register* 57, April 15, 1992) established another mechanism, "Parallel Tracking," to make available promising new investigational drugs as soon as possible to persons with AIDS or HIV-related diseases. The mechanism enables recipients who are not able to participate in ongoing clinical trials and who are not able to take standard therapy or for whom standard therapy is no longer effective to have access to promising new investigational drugs without a concurrent control group to monitor drug safety. These patients are treated in parallel with the principal controlled investigations.

The IRB must satisfy both FDA and DHHS regulations in cases where FDA and DHHS have jurisdiction over the nature and extent of care provided in critical care situations. In instances in which the FDA waives the requirement for prior IRB approval (see FDA regulations cited above), an institution may still be required by DHHS to have prior local IRB approval; these occur when the institution holds an MPA or when research is supported by a DHHS department or agency. Furthermore, even if FDA gives the institution the right to waive local IRB approval, the institution may still require local approval.

Emergency/critical medical care is currently a very controversial issue. The following Office for Protection from Research Risks (OPRR) report *(Figure 10a)* and FDA statement *(Figure 10b)* provide further guidance on this topic. Unless the research in question is covered under the FDA regulations, DOE assumes the same position as stated in OPRR Reports 91–01 shown in Figure 10a.

Figure 10a. OPRR Reports, 91–01

Number 91–01
(Human Subject Protections)

OPRR Reports

May 15, 1991

Subject: Emergency Medical Care

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) chairs throughout the country. Its purpose is to clarify requirements in the DHHS regulations for the protection of human research subjects (45 CFR Part 46) concerning provisions for emergency medical care.

Your attention is called to two provisions in the regulations. First, 46.116(f) states: " . . . *nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care . . .*" This provision makes it clear that the regulations are **not** intended to interfere with the provision of emergency care for patients who need such **care**. Second, 46.103(b) states: *"The Department will conduct or fund research covered by these regulations only if the institution has certified to the Secretary that the research has been reviewed and approved by an IRB . . ."* This provision calls for IRB review and approval **prior** to initiation of the **research**.

These regulatory provisions accomplish two objectives. The first objective is to make clear that emergency medical **care** for **patients** may be provided without regard to IRB review and approval. The second objective is to require IRB review and approval prior to initiation of **research** involving human **subjects**. Confusion can arise when both objectives appear to pertain to the needs of the same person. The National Institutes of Health's (NIH) Office for Protection from Research Risks (OPRR) is, therefore, providing the following clarification. Whenever emergency care is initiated without prior IRB review and approval, the patient may **not** be considered to be a **research subject**. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. Simply stated: DHHS regulations for the protection of human subjects do not permit **research** activities to be started, even in emergency, without prior IRB review and approval.

If the emergency care involves drugs, devices, or biologics that are considered to be investigational by the Food and Drug Administration (FDA), then it may be necessary to meet FDA requirements to use the investigational article for emergency purposes.

Continued—

Figure 10a. OPRR Reports, 91–01 *(continued)*

Page 2

OPRR believes that a number of institutions have not clearly understood these requirements. Each institution is therefore requested to review its procedures and, if necessary, to modify them in order to come into compliance with these requirements. Furthermore, institutions with approved Multiple Project Assurances should modify them as necessary to reflect the interpretation of the regulations set forth above.

Modifications should be forwarded to the Assurance Branch; Division of Human Subject Protections, OPRR; Building 31, Room 5B-59; National Institutes of Health; Bethesda, Maryland 20892—Attn. Dr. Duncan.

Your attention to this important matter is greatly appreciated.

F. William Dommel, Jr., J.D.
Director
Division of Human Subject Protections
Office for Protection from Research Risks

Charles R. McCarthy, Ph.D.
Director
Office for Protection from Research Risks

Figure 10b. U.S. Food and Drug Administration, Emergency Use of an Investigational Drug

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

February 1989

EMERGENCY USE OF AN INVESTIGATIONAL DRUG

Emergency use is defined as the use of a test article (e.g., investigational drug or biologic) 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 Institutional Review Board (IRB) approval.

When a situation arises that, in the judgment of a physician, calls for the emergency use of an investigational drug or biologic in a single patient, an IND is still necessary. The situation may arise when a patient does not meet the criteria of a study protocol, or where an approved study protocol does not exist. The usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for use (in this one patient) under the company's IND. Should the company elect not to name the physician as an investigator the physician can contact FDA directly for an IND.

The physician will be placed in contact with an FDA physician familiar with the drug or biologic to review the proposed circumstances for use and the information to be submitted in the IND.

Emergency use of an investigational drug or biologic product may be exempt from FDA requirements for IRB review provided that such emergency use is reported to the IRB at the institution within 5 working days. Any subsequent use of the investigational product at the institution is subject to IRB review. The investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who are not otherwise participating in the clinical investigation certify in writing all of the following:

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained 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.

D. Adverse Event Reporting

An adverse event or effect is an undesirable and unintended, though not unexpected, result of therapy or intervention. In a research setting this includes most instances where a subject experiences an undesirable effect that was previously described in the consent form. Examples include feeling faint after having blood drawn, chest pains after being on a treadmill, or emotional upset after completing a probing questionnaire. Actual injury to a subject is an extreme form of adverse event.

> ***Adverse Event**—An undesirable or unintended, although not necessarily unexpected, result of therapy or other intervention.*

Adverse events may be reported by either the subject or the researcher. All consent forms for studies of greater than minimal risk should include an advisory on how a subject may contact the IRB in case of injury related to the research. Researchers should be instructed to report all adverse events to the IRB regardless of the event's perceived severity. Researcher reports should be immediate, preferably by telephone call to the IRB office or chairperson with a follow-up in writing.

In the case of injury requiring treatment, the researcher, the IRB, and the institution must act quickly to ensure that adequate medical care is provided to the subject. This is both an ethical imperative and a requirement of the Federal regulations. Provision of such care is greatly facilitated by considering the possible provision of emergency medical care in the original protocol design. This is particularly important when biomedical research is conducted outside of a hospital environment.

The IRB should convene to investigate and consider the event/effect and appropriate response. IRBs typically consider the following points in reviewing an event:

- How severe was the effect on or injury to the subject?
- Was the subject properly informed of this potential risk in advance?
- Did the researcher have an adequate procedure for dealing with the event, and, if so, was the procedure followed?
- Should the experimental protocol be changed to make such events less likely in the future? Or, should the protocol be discontinued immediately?
- Is the event isolated or is it part of a pattern?

The spectrum of IRB response to an event ranges from simple written acknowledgement of an event through request for corrective action. Very severe injuries or those to which the investigator responded inappropriately can and should lead to temporary or permanent suspension of research approval by the IRB.

In general, it is the IRB that decides whether an event/effect should be reported to the assuring and funding agencies. Any effect or injury that is not transient and/or that requires medical treatment of the subject is generally considered to be reportable. Any event or effect that results in suspension of research approval *must* be reported. Funding agencies or sponsors may set criteria for reportable events that are broader than those generally used by the IRB. Pharmaceutical companies, for example, increasingly require that all injuries or deaths among study participants be reported to the sponsor even when the injury is not clearly linked to the study (e.g., automobile accidents). Any report made to the funding agency or sponsor should also be copied to other bodies to whom the IRB reports.

Reports must be made to the assuring agency and the funding agency. Additionally, if the research takes place at a DOE facility or using DOE personnel or materials, adverse events should be reported to the DOE Human Subjects Program Manager. Adverse events involving studies covered by a Food and Drug Administration (FDA) Investigational New Drug or Device (IND) permit or studies falling under the review of a Radioactive Drug Research Committee must also be reported to the FDA. Additional reporting requirements may exist depending on state, local, and facility regulations.

E. Unforeseen Risk

Not all risks will be or can be known at the time research is initiated. Events that cannot be reasonably predicted are termed unforeseen risks. For example, the equipment used in an experimental procedure could fail, resulting in direct physical injury to the subject or exposing the subject to a potential danger (e.g., radiation). While unforeseen risk is usually considered in association with complex biomedical research, examples can be found in far less invasive environmental and energy research. A relevant example would be the use of a compound or biologic believed harmless at the time of the experiment but later discovered to have potential human health consequences.

Unforeseen Risk and the Informed Consent Process

Unforeseen risks should be considered as part of the consent process. Three elements are commonly included:

- A statement informing the subject about the possibility of some risks that may not be known at the time they consent to participate.
- A statement that the researcher is obligated to inform subjects of findings relevant to the subject's health.
- The institution's statement on compensation for injuries incurred in research that should cover both known and unforeseen risks.

Subjects [must] be informed that not all risks are predictable and that they will be informed of risks uncovered in the future that might affect them.

The Environmental Protection Agency has drafted a particularly explicit statement for consent forms that includes the first two elements: "I understand that while all risks known at this time have been discussed above, other unforeseen risks may occur or be revealed during future studies. In the event that the investigators in this study find in the future that there was a potential risk to me, unknown at the time of my participation in the study, and such risk is other than insignificant and might have some bearing on my health status, I will be informed."

The University of California at San Francisco recommends the following language for biomedical studies: "The experimental treatments may have side effects that no one knows about yet. The researchers will let me know if they learn anything that might make me change my mind about participating in the study."

The common thread between these advisories is that subjects must be informed that not all risks are predictable and that they will be informed of risks uncovered in the future that might affect them.

The IRB should establish policies on when such warnings on unforeseen risk should or must be included in consent forms. Although the consensus is to include such warnings in therapeutic biomedical protocols, considerable variation on what other types of studies should include these warnings can be found from institution to institution.

Discovering New Risks

When a new risk to subjects is uncovered, it must be promptly reported to the IRBs overseeing the study. This report must be made whether or not the consent form informed subjects about unforeseen risk. The IRB should convene to consider the appropriate response. IRBs typically consider the following points when deciding if and how to inform the subjects:

- Is the risk significant?
- Is the risk likely to affect the health of the subject?
- Is the potential for psychological harm to the subject greater than the physical health risk?

In considering this last point, committees should take care to note the current general trend towards notification and away from paternalism. The nonscientist and public members of the committee should play prominent roles in determining the final course of action.

If it is agreed that subjects should be notified, the focus should be on minimizing the anxiety caused by the notice itself. A plan for the personal notification of subjects should be developed. Identifying and locating subjects may require substantial resources. Subjects should be notified as promptly and with as much concurrence as possible to prevent inadvertent "notice" via the press or hearsay. Both physician and counseling support should be provided when needed, with the costs covered in a manner consistent with the institution's policy on reimbursement for injury.

F. Liability: Compensation for Injury

Although the regulations for protection of human subjects require some discussion of compensation for injuries that may be suffered in the course of a research project, they do not determine *how* such compensation is provided, or even *whether* it is provided. Therefore, each institution is free to decide on a project-by-project basis the extent of compensation for research-related injuries.

Factors that should be considered are—

- The likelihood and potential severity of harm to the subject. If the project is research on artificial hearts, compensation for injury would be more likely than in a study of ergonomic furniture to reduce lower back pain.

- The benefit to the individual. If the project provides much sought-after treatment of an otherwise incurable ailment, compensation would be less likely than for injuries received by a subject who was testing a device for use by others.

- The availability of a sufficient pool of research subjects. If the research project has a shortage of applicants, one inducement might be to offer compensation for injuries.

- The financial resources of the project and the institution to provide compensation for research-related injuries. At a major medical center, such compensation is more readily available than at a smaller, private foundation.

If an institution decides to compensate research subjects, it must then determine the *extent* to which an individual will be compensated. Many institutions that do provide compensation limit it only to "physical injury" so as to preclude claims for mental (pain and suffering), social (loss of reputation), or consequential (loss of time; inability to qualify for a particular job, etc.) injuries, the cost of which can easily be hundreds or even thousands of times larger than the direct physical damages.

Below are examples of how some institutions have dealt with the subject.

Sample Statements About Compensation

University A: "Policy regarding research-related injuries. In the unlikely event of physical injury resulting from research procedures, the University will provide first-aid medical treatment. Treatment [for] injuries or side effects directly related to this experimental treatment will be provided at no cost to you. Additional medical treatment will be provided in accordance with the determination by the University of its responsibility to provide such treatment. However, the University does not provide compensation to a person who is injured while participating as a subject in research."

University A, as revised in response to advice from the local IRB: "I understand that money for research-related side effects or harm or for wages or time lost is not available. Necessary emergency medical care directly related to this treatment will be provided by _____, M.D."

Institution B: "Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the National Institutes of Health, Clinical Center, nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law."

University C: "NOTE: Immediate necessary care will be provided without charge by _____ University if you are injured because of participation in this research project. However, there is no provision for the costs of further medical care or for the monetary compensation for such injury."

University D: "I have been informed that should I suffer any injury as a result of participation in this research activity, reasonable medical facilities are available for treatment at this institution. I understand, however, that I cannot expect to receive any credit or reimbursement for expenses from this institution or any financial compensation from this institution for such injury."

University E: "I understand that in the event of physical injury resulting from this research, the University of _____ Hospitals will provide me with free emergency care, if such care is necessary. I also understand that if I wish, the University of ____ Hospitals will provide non-emergency care, but the Medical Center assumes no responsibility to pay for such care or to provide me with financial compensation."

G. Types of Research That May Not Require IRB Review

Management Tools

Institution management and staff often use surveys, data analyses, and other tools in improving operational processes, procedures, and programs. These tools do not constitute "research" so long as data are considered in the aggregate, i.e., are not personally identifiable, and the intent is for improvement in operational effectiveness.

Quality Tools

In the performance of work, many organizations utilize a variety of quality tools to help assess work quality. Examples include customer surveys, benchmarking studies, and performance metrics. Measurements and information obtained for the purpose of process improvement and project management may not be considered as research from the perspective of 10 CFR 745.

Dissertations

Students pursuing master's and doctoral degrees often are required to complete an approved thesis as part of their graduate curriculum. Any research they conduct that involves human subjects or personally identifiable data and is supported by the institution (by any paid time, materials, facilities, services, or funds) requires IRB review. Any other research that is conducted without institutional assistance is usually under the purview of the sponsoring academic institution and is reportable to that institution. The solicitation of an institution's employees as study participants or the use of employee data in research may require institutional management approval but not necessarily IRB review.

Special Classes of Subjects: Vulnerable Populations

A. Introduction

Federal regulations require that institutional review boards (IRBs) give special consideration to protecting the welfare of vulnerable subjects such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. *(See 10 CFR 745.111.)* Research subject to Department of Health and Human Services (DHHS) regulations must comply with specific provisions on research involving fetuses, pregnant women, and human in vitro fertilization (45 CFR 46, Subpart B); prisoners (45 CFR 46, Subpart C), and children (45 CFR 46, Subpart D). In general, the special regulations allow IRBs to approve research that entails minimal risk or that will benefit the subjects directly. Investigations involving these subjects that present greater than *minimal risk* without directly benefitting to them must be reviewed and approved by the Secretary of DHHS in consultation with appropriate experts. Although the Department of Energy (DOE) has not formally adopted subparts B, C, and D, it is highly recommended that all DOE investigators and IRBs become familiar and comply with these specific requirements.

Although DOE has not formally adopted subparts B, C, and D of 45 CFR 46, it is highly recommended that all DOE investigators and IRBs become familiar and comply with these specific requirements.

Identifying Vulnerable Subjects

Vulnerable persons are compromised in their ability to give informed consent. Vulnerability may characterize students, employees, patients in emergency rooms, institutionalized persons, and people who are not fluent in English. If a person is in a situation in which his or her ability to give informed consent is compromised or eliminated, that person is vulnerable. The IRB plays a vital role in identifying vulnerable subjects and ensuring their protection. The IRB Guidebook published by the DHHS Office of Protection from Research Risks (OPRR) provides specific guidance on 12 categories of subjects: fetuses and human *in vitro* fertilization, women, children and minors, cognitively impaired persons, prisoners, traumatized or comatose patients, terminally ill patients, elderly/aged patients, minorities, students, employees, and normal

***Minimal Risk**—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 examination or tests.*

volunteers. The discussion on specific vulnerable populations in sections B, C, and D of this chapter relies heavily on the OPRR Guidebook.[1]

Including Vulnerable Populations

Reference Materials Included in This Chapter

- OPRR Reports, 94–01 (Figure 11a).
- OPRR Reports, 93–04 (Figure 11b).
- *Medical News & Perspectives*, JAMA, April 28, 1993 (Figure 11c).

Exclusion of one gender, a race, or another class of human subjects is not an appropriate way to ensure protection of vulnerable subjects. In fact, exclusion of certain populations from products developed at research facilities may result in data that cannot be widely and safely used. A policy issued by the DHHS National Institutes of Health (NIH) states that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of NIH that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Clinical research that is funded by DOE, performed at DOE facilities, or performed by DOE personnel, should also follow this direction.

Reference materials regarding the inclusion of vulnerable populations in research are included in this chapter. Figure 11a is an OPRR report dated April 25, 1994, on the inclusion of women and the minorities in research. Figure 11b, also an OPRR report, provides information on the Food and Drug Administration (FDA) guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. Figure 11c is an article entitled "FDA Lifts Ban on Women in Early Drug Tests, Will Require Companies to Look for Gender Differences."

Protecting Vulnerable Populations

"IRBs are responsible under the Common Rule for protecting vulnerable populations that participate in research. At a minimum, when IRBs review research that may involve members of any vulnerable population, someone who knows that population should participate in the review.

"Following are additional ways in which IRBs can ensure the protection of vulnerable populations in research. IRBs can—

- Encourage understanding of informed consent as an interactive process, not just a document.
- Insist on the subjects' freedom to ask questions and to withdraw at any point.
- Stress the use of the appropriate language and the need for sensitivity to cultural nuances.
- Adopt the use of "consent monitors" or special advocates for those who are impaired.

[1] *OPRR 1993 Protecting Human Research Subjects Institutional Review Board Guidebook.*

- Promote better understanding of vulnerable populations within the research community.
- Be vigilant to prevent coercion and undue inducement (whether payment or other rewards)."[2]

Assurances from DOE institutions should include a statement of compliance with Subparts B, C, and D. DOE institutions holding NIH MPAs are already required to include this in their assurance. For example:

> [Institution] shall comply with the special policies of the regulations of the Department of Health and Human Services (DHHS) for research involving fetuses, pregnant women, human in vitro fertilization, prisoners and children, and shall consider additional safeguards in research involving individuals institutionalized as mentally disabled and other potentially vulnerable groups.

[2] *Protecting Human Subjects*, Office of Health and Environmental Research, U.S. Department of Energy, Fall 1994, p.5.

B. Fetal and Human In Vitro Fertilization Research

> ***Human In Vitro Fertilization**—Any fertilization involving human sperm and ova that occurs outside the human body.*

Research involving the human fetus raises special concerns for IRB reviewers. The fetus has a unique and inextricable relationship to the mother. The fetus may be an indirect subject of research when women who may be pregnant participate in studies. It cannot consent to be a research subject. These circumstances have aroused lengthy public debate on the ethics of fetal research and led to special regulations that guide IRB deliberation about fetal research. These regulations are included in 45 CFR 46, Subpart B. Subpart B is now under consideration for revision by DHHS, but at the time this handbook was prepared, the revisions had not been completed.

Points To Consider for Fetal and Human In Vitro Fertilization Research

1. Is animal research an appropriate prerequisite? Has it been completed? Where appropriate and feasible, has research with nonpregnant women been completed?

2. If there is any risk to a fetus, is the information sought judged to be important? Could it be obtained by any other means?

3. Is risk to the fetus minimal?

4. In research with a nonviable fetus ex utero, is any intervention proposed that would shorten or prolong the natural course of dying?

5. Are the investigators involved in any decisions about an abortion process (e.g., timing or method) that is related to the research?

6. Is abortion encouraged for research purposes (e.g., are free care or services offered)?

7. Do any applicable Federal, state, or local laws restrict such research?

8. From whom must consent be obtained?

C. Women

> ***Pregnancy***—*The period from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but for research purposes, investigators presume that a living fetus is present until evidence to the contrary is clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes necessary a definition of pregnancy based on implantation.*

Special regulations (45 CFR 46, Subpart B) govern the participation of pregnant women in research. Research involving women who are or may become pregnant requires special attention from IRBs because of women's additional health concerns during pregnancy. Special attention is also justified because of the involvement of a third party, the fetus, who may be affected but cannot give consent, and because of the need to avoid unnecessary risk and to prevent harm or injury to future members of society. Among other considerations, IRBs must determine when the informed consent to the research must be obtained from the father. Pregnant women may be involved in several categories of research. IRB duties differ for each category, but the primary objectives are assessing (1) whether the research is directed toward the mother's health or toward the fetus and (2) what the risks are to the woman and to the fetus or infant. Research directed toward the fetus is discussed in the previous section. Federal regulations provide that no pregnant women may be involved as a subject unless either (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.

Inclusion of women in study populations is a relatively new policy for both NIH and FDA. NIH policy requires the inclusion of women and minorities in research study population so that research findings can benefit all persons at risk of the disease, disorder, or condition under study. *(See Figure 11a, April 25, 1994, OPRR report entitled "Inclusion of Women and Minorities in Research." Figures 11b and 11c provide further guidance on the inclusion of women in research.)*

Points To Consider for Research Involving Women

1. For all studies, is there reason to exclude pregnant or lactating women? If so, how strict should the screening measures be?

2. For all studies involving pregnant women, have appropriate studies on animals and nonpregnant humans already been conducted? Is any special monitoring of the informed consent process needed?

3. For studies directed toward maternal health, is the risk to the fetus the least possible consistent with the research objectives? Will the mother be adequately informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?

4. For studies of pregnancy, labor, or delivery, is the risk to the fetus "minimal"? Is the father's consent required?

5. For studies of lactating women, is the supply and content of breast milk adequately protected?

6. For studies of conception or contraception, are the risks, benefits, reversibility, and alternatives adequately explained? In contraceptive studies, is there adequate explanation of possible failure and of the options available for dealing with unintended pregnancies?

7. Will women be appropriately represented in the study? Does the study need to be designed to allow evaluation of gender differences?

Figure 11a. OPRR Reports, 94–01

Number 94–01
Human Subject Protections

OPRR Reports

NIH PHS HHS

April 25, 1994

Subject: Inclusion of Women and Minorities in Research

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) Chairs throughout the country. It transmits new National Institutes of Health (NIH) Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (Federal Register, 59FR14508, March 28, 1994; also published in the NIH Guide for Grants and Contracts, Vol. 23, Number 11, March 18, 1994)* and offers points to consider based on these guidelines and responsibilities under the Department of Health and Human Services (DHHS) regulations for protection of human subjects (45 CFR 46).

IRBs have long had as part of their responsibilities examining issues of justice and determining equitable selection of subjects in accordance with The Belmont Report and the regulations for protection of human subjects (45 CFR 46.111(a)(3)). The inclusion of both women and men and of minorities in research is important, both to ensure that they receive an appropriate share of the benefits of research and that they do not bear a disproportionate burden. To the extent that participation in research offers direct benefits to the participants, underrepresentation of men, women or minorities denies them the opportunity to benefit. Moreover, for purposes of generalizing research results, investigators must include the widest possible range of population groups.

Institutions have a responsibility to create an environment in which equitable selection of research participants is fostered. In so doing, they must support their IRBs and investigators in goals of increasing participation of women and minorities in research trials. Institutions must empower IRBs to fulfill the mandates of the NIH Guidelines and their regulatory responsibilities. They are called upon to promote and support effective recruitment strategies and communication mechanisms to ensure policy implementation.

Seven points to consider in deliberations about appropriate selection of research participants are offered. Institutions and IRBs have responsibilities, as follows:

- To help ensure that investigators understand the importance of inclusion of both genders and minorities in research and clearly delineate the expectations for the design and conduct of such research. They should assist in providing investigators with written guidance and educational opportunities for clarification.

Continued—

*Not included.

Figure 11a. OPRR Reports, 94–01 *(continued)*

- To specify that, when scientifically appropriate, investigators cite evidence or lack of evidence if a health situation or intervention in the proposed research may affect one gender or minority group differently and describe how the proposed research addresses that evidence. Investigators should be prepared to describe the extent to which both genders and persons of various ethnic and racial backgrounds are or have been involved in similar research.

- To help create guidelines for investigators to facilitate recruitment and retention of participants to ensure representation and sufficient involvement of targeted populations. The extent to which investigators are collaborating with those at other institutions that can involve increased numbers of men or women or populations from different minority groups must be a part of the information the IRB reviews, particularly with regard to Phase 3 clinical trials.

- To ensure that any special vulnerabilities of participants (e.g., educational level, socioeconomic status) are accounted for and handled appropriately. The IRB should carefully consider if reimbursements (cash or material provisions) are appropriate to the context of the proposed research, with special attention that these reimbursements do not promote coercion or undue influence to participate or to remain in a study.

- To safeguard the consent process and to promote open and free communication between the researcher and the participants. Investigators and IRBs must seek to understand cultural nuances and types of foreign languages inherent in the populations to be enrolled. The possibility of illiteracy of a potential research participant must also be considered and assurances given that adequate provision has been made for appropriate translations of the consent documents or the availability of translators.

- To arrange for inclusion of women and members of minority groups on the IRB, especially if the nature and volume of the research to be conducted at the institution routinely includes these populations. IRBs should also consider consulting ad hoc advisors who could help with understanding the perspectives of various groups. Also, institutions and IRBs can encourage investigators to seek out such perspectives during planning of research protocols.

- To specify that NIH-supported investigators provide details of the proposed involvement of humans in the research, including the characteristics of the subject population, anticipated numbers, age ranges, and health statuses. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review numbers are not included in the background data for a protocol, the investigators must provide a clear rationale for exclusion of this information.

The enclosed Federal Register notice* includes the NIH Guidelines, based on provisions in the NIH Revitalization Act of 1993 (Public Law 103–43), on the inclusion of women and minorities and their subpopulations in clinical research conducted or supported by NIH. Some of the other Federal Departments and Agencies that conduct or support research involving humans currently have mandates in their statutes or congressional committee reports similar to those given by the Congress to NIH. Institutions must determine the extent to which they will apply the specific requirements of the enclosed Federal Register* notice to research other than that conducted or supported by NIH.

Continued—

*Not included.

Figure 11a. OPRR Reports, 94–01 *(continued)*

The definition of "clinical research" in the NIH Guidelines includes all research involving humans, even that which is exempt from IRB review in accordance with 45 CFR 46. The Guidelines do not require IRBs to review research which is exempt under 45 CFR 46, however.

The NIH Guidelines indicate the circumstances under which various populations must be included in clinical investigations, with special criteria for Phase 3 clinical trials. The Guidelines refer to a "clinical trial" as a broadly-based prospective Phase 3 clinical investigation for the purpose of evaluating an experimental intervention that is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. (See Section V.A of the enclosed NIH Guidelines.) If data from prior studies indicate that there are differences between the genders or among racial/ethnic groups in the proposed research, or if there are no data to support or to negate differences, Phase 3 clinical trials will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups, so that analysis of detected trends in the affected subgroups can be performed. If prior evidence indicates that the results will not show gender or racial differences, researchers are not required to use gender or race/ethnicity as selection criteria for study subjects. They are, however, encouraged to include these groups. (See Section III.B of the enclosed NIH Guidelines.*)

IRBs are empowered by 45 CFR 46, the DHHS assurances to comply with 45 CFR 46 under which they operate, and the NIH Guidelines, to approve, request modification of, or disapprove research based on their review and assessment of the extent to which the analysis criteria specified in the NIH Guidelines will be met in the proposed research.

OPRR encourages you to direct questions and comments about the new NIH Guidelines to the NIH Office of Research on Women's Health (301-402-1770) or the NIH Office of Research on Minority Health (301-402-1366) and to the contact points listed in the enclosed Federal Register notice.*

Gary B. Ellis, Ph.D.
Director
Office for Protection from Research Risks

Enclosure

*Not included.

Figure 11b. OPRR Reports, 93–04

Number 93–04
(Human Subject Protections)

OPRR Reports

NIH PHS HHS

August 13, 1993

Subject: Food and Drug Administration Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs

Dear Colleague:

This letter is being forwarded to Institutional Officials and Institutional Review Board (IRB) chairs throughout the country to notify you of the issuance of the Food and Drug Administration (FDA) "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." A copy of the Notice of the Guideline published in the Federal Register on July 22 (56FR39406) is enclosed.* This guideline sets forth FDA's expectations regarding inclusion of both genders in drug development and revises the section "Women of Childbearing Potential" in the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs" [HEW Publication No. (FDA) 77-3040].

There are two major changes addressed in this guidance. First, FDA is withdrawing the restriction on the participation of women of childbearing potential in early clinical trials, including clinical pharmacology studies and early therapeutic studies. Second, FDA is formalizing expectations regarding inclusion of subjects of both genders in drug development; analyses of clinical data by gender; assessment of potential pharmacokinetic differences between genders; and, where appropriate, assessment of pharmacodynamic differences and the conduct of specific additional studies in women.

A major effect of the new guideline is to give more flexibility to IRBs, investigators, and subjects in determining how best to ensure the safe participation of women of childbearing potential in clinical studies. Changes in FDA policy reflected in the new guideline remind us of the importance of the IRB deliberative process, the informed consent document and process, and the necessity for attention to the completeness and accuracy of information conveyed to potential and enrolled subjects. Women must receive adequate information and opportunity for discussion regarding, for example, potential risks to their fertility and possible teratogenic potential of the drugs and biologics. Your attention to this important matter is greatly appreciated.

Gary B. Ellis, Ph.D.
Director
Office for Protection from Research Risks

Enclosure

*Not included.

Figure 11c. ***Medical News and Perspectives*, JAMA, April 28, 1993**

FDA Lifts Ban on Women in Early Drug Tests, Will Require Companies to Look for Gender Differences

NEW POLICIES at the Food and Drug Administration (FDA) should substantially aid the understanding and advancement of women's health issues.

The date of the official announcement and policy change had not been set at press time. But Eileen Leonard, M.D., of the agency's Center for Drug Evaluation and Research, confirms that the rule against including fertile women in early clinical trials, enacted in 1977, is being lifted.

"We are increasingly aware that there are approaches to ensuring the safety of the fetus other than completely excluding women of childbearing potential," says Leonard. Other precautions can be taken, such as informing women of the risks, ensuring that they practice contraception, doing pre-enrollment pregnancy testing, and the like, she says.

'Other Players'

"Also, we recognize that there are other players in clinical trials who should have a say in that decision. Clearly the women, the investigators, and IRBs [institutional review boards] should be involved in deciding whether there are fetal risks and how they should be handled, rather than the FDA just making the decision," says Leonard.

There are scientific reasons for lifting the ban as well. Exclusion of women from early trials has meant that any important gender-related differences were not found until late in drug development, if then. "You miss an opportunity to use that information to affect the design of the critical trial," Leonard says. For example, if women are found to respond to a lower dose of a drug, "you would like to know that before starting a phase III trial with a dose that might be too high for them. So scientifically it's optimal to include women from the earliest stages of drug development.

Perhaps even more significant will be the new requirement that pharmaceutical manufacturers conduct thorough analyses of their data in order to discern any gender differences during drug development.

Now, even in cases where women are currently included in studies, "the sponsors aren't necessarily conducting the appropriate analyses to see whether there are gender-related differences," Leonard says.

The new policy will "make clear that it is going to be expected prior to drug approval that any significant gender differences be identified."

The Pharmaceutical Manufacturers Association (PMA) is withholding comment on the policy change until it is official. Spokesman David Emory says, "We will be happy to talk when we see it in the *Federal Register*."

When asked a year ago about the efforts of women's health activists to get more women into trials, PMA special populations committee chair Lionel Edwards, M.D., warned that a "blanket inclusion of women in every study would put them and their unborn children at unnecessary risk, while making medicines more costly because longer, more complex trials would be needed and data analysis would be more extensive." A case-by-case review should be done, he advised, to "determine where it is necessary to include women in trials."

'Technical Barrier'

The FDA's pending policy change means that there is "one less barrier" to women, but it is "just sort of a technical barrier," says Florence Haseltine, M.D., Ph.D., director of the Center for Population Research at the National Institutes of Health (NIH), Bethesda, Md. "People cannot cite the FDA rules anymore to exclude women." Still, other "real barriers are much more substantial," she says.

While risk to fetuses is a real issue, it is also something "people have hidden behind," says Jean Hamilton, M.D., a professor of sociology, health sciences, and women's studies at Duke University, Durham, N.C. "There has always been a substantial population of women not at risk for pregnancy," she says, noting that as many as one third of women in the United States have undergone hysterectomies, and that others have had tubal ligations or have partners who had vasectomies. "It's really been kind of an excuse."

Women have tended to be excluded from clinical trials even when a large population of women might have been able to participate, says Hamilton. She cites a review of trials of drugs for acute myocardial infarction that found that fewer than 20% of randomized subjects could be identified as women (*JAMA*,1992;268:1417—1422). This was true even though, as the authors of that article wrote, the traditional explanations for excluding women—such as risk to the fetus, hormonal fluctuations, protective cardiovascular effects of estrogen, and reduced statistical power due to the slower rate at which women develop cardiac problems—"would have little relevance to the vast majority of female acute myocardial infarction patients.

Recruit and Retain

With the pending policy change at the FDA, "now we need to figure out what we're going to do to actually recruit women and get them to stay in studies," says Hamilton.

Some research, including her own, suggests that women drop out of some trials more often than men. Other issues have contributed to women's relatively low participation, she says. These include male researchers "trivializing" women's concerns as well as not making provisions for the "burden of child care and elder care, which may indeed make it more difficult for women to participate."

Teratogenicity, difficulty in taking the menstrual cycle into account, and higher costs were reasons for excluding women that "may have seemed reasonable at the time they were put forth. They aren't reasonable anymore," says Judith H. LaRosa, Ph.D., deputy director of the NIH's Office of Research on Women's Health. "They are factors that must be considered, but certainly they aren't an excuse for excluding women."

LaRosa adds that while it may seem less expensive to exclude women, "in the end it is much more expensive" to pay for the clinical consequences of not knowing about gender-related differences.

The Office of Research on Women's Health recently sponsored 2 days of hearings on the recruitment and retention of women in clinical trials. LaRosa says that beyond the issues of fear for the fetus and distrust of researchers, the problems that came to the fore were a lack of transportation, time off work, and care of children and the elderly.

What is needed, she says, is to teach people who put trials together to take these things into account, and to make sure they include people in the communities they intend to study in discussions of the design of those studies.

"When someone says to me women are so difficult to recruit, my response is, not if you know how," LaRosa concludes.

——by Paul Cotton

JAMA, April 28, 1993—Vol. 269, No. 16

D. Prisoners

> ***Prisoner**—An individual involuntarily confined in a penal institution, including persons (1) sentenced under criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (for example, for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].*

The involvement of prison inmates in research was once common because the stability of prison life (for example, controlled diet and ready availability of subjects for followup) made prisons attractive research environments. More recently, however, ethicists and others concerned with the treatment of human participants in research have recognized that the very fact of incarceration may make it difficult or impossible for prisoners to give voluntary informed consent. In response to this growing concern, the National Commission for the Protection of Human Subjects considered this problem and issued its report and recommendations in 1976. In 1978, DHHS issued specific regulations governing research with prisoners (45 CFR 46, Subpart C). The implementation of FDA regulations on research involving prisoners has been delayed until further notice. Some Federal agencies, for example, Federal Bureau of Prisons, significantly limit the involvement of prisoners in biomedical research.

When a protocol proposes to use prison inmates as a study population, the first question IRBs must ask is whether that population was chosen simply out of convenience to the investigator. It should ask whether the nature of incarceration conflicts with the ethical principle of autonomy captured in the Nuremberg Code. This provision requires that the subject 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 forms of constraint or coercion. A second issue is whether confidentiality of participation and of data can be adequately maintained in the prison. Yet another question is whether prisoner subjects can ethically be paid for participation and, if so, how much. Paying prisoners the same amount that would be paid to nonprisoners may be seen as unduly influential in a setting where inmates can earn only a small fraction of that amount for any other work activity.

If the IRB knows that it will be reviewing protocols involving prisoners as subjects, IRB members should familiarize themselves with 45 CFR 46, Subpart D, and discuss these regulations before any actual prisoner protocols are presented, regardless of whether the research is conducted under the auspices of DHHS or DOE.

Points To Consider for Research Involving Prisoners

1. Does the IRB include at least one member who is a prisoner or a prisoner representative?

2. Does the proposed research fall within one of the permissible categories of research with prisoners?

3. Is the use of prisoners as subjects justified?

4. Is there any evidence of duress, coercion, or undue influence in the particular prison(s) from which subjects will be recruited? (Does the prison facility meet all of the conditions set forth in applicable regulations?)

5. Are there any applicable state laws with which the IRB must comply? Note, too, that the Federal Bureau of Prisons places special restrictions on research that takes place within the Bureau of Prisons. *(See 28 CFR, Part 512.)* The restrictions apply to any research involving inmates in the custody of the Attorney General and assigned to the Bureau of Prisons, regardless of the institution in which the inmate is incarcerated.

E. Children and Minors

> ***Children***—*Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402(a)].*

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations are in place for reviewing research involving children. Research that is contrary to the rights and welfare of child subjects is prohibited. A good summary of the ethical consideration surrounding research involving children can be found in Levine (1989).[3] The regulations are in 45 CFR 46, Subpart D, and DOE investigators and IRBs should assure compliance with these regulations.

> ***Benefit***—*A valued or desired outcome; an advantage.*
>
> ***Risk***—*The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."*

IRBs reviewing research involving children as subjects' must consider the benefits and discomforts inherent in the proposed research and determine whether the discomforts are justified by the expected benefits to the child subject or to society as a whole. In calculating the degree of risk and benefit, the IRB should weigh the circumstances of the subjects under study, the magnitude of risk that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects. Federal regulations require IRBs to classify research involving children into one of four categories and to document their discussion of the risk and benefits of the research study. The four categories are as follows:

1. Research involving no more than minimal risk.

2. Research involving more than minimal risk, but presenting the prospect of direct benefit to the individual subject. Research in this category is approvable provided it meets the following conditions:

   a. The risk is justified by the anticipated benefit to the subject.

   b. The relationship of risk to benefit is at least as favorable as any available alternative approach.

   c. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

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[3]Levine, Robert J. "Children as Research Subjects." In *Children and Health Care: Moral and Social Issues,* edited by Loretta M. Kopelman and John C. Moskop, pp. 73–87. Boston: Kluwer Academic, 1989.

3. Research involving greater than minimal risk with no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided it meets all the following conditions:

   a. The risk represents a minor increase over minimal risk.

   b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with ones they are likely to undergo in their actual or expected medical, dental, psychological, social, or educational settings.

   c. The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition.

   d. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

***Assent**—A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent [45 CFR 46.402(b)].*

***Permission**—The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].*

***Guardian**—An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(3)].*

***Emancipated Minor**—A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage, or procreation.*

***Mature Minor**—Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor.*

4. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research that is not otherwise approvable may be conducted or funded by DHHS or DOE provided the IRB and the cognizant agency secretary, after consultation with panels of experts, finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The panel of experts must also find that the research will be conducted in accordance with sound ethical principles. Adequate provisions must be made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408.

When children or minors are involved in research, both the assent of the child or minor and permission of the parents are required in place of informed consent of the subject. Because children have not reached their full intellectual and emotional capacities and are legally unable to give valid consent, their involvement in research requires the permission of parents or legally authorized representatives. The IRB must determine whether the permission of both parents is necessary and, if not, the conditions under which one parent may be considered not reasonably

available. The IRB must also determine that adequate provisions are made for soliciting the assent of the children when the IRB judges that the children are capable of providing assent.

Points To Consider for Research Involving Children and Minors

1. Does the research have an identifiable prospect of direct benefit to the individual child participant? Can that benefit be achieved through alternative means?
2. Does the research have an identifiable prospect of risk to the individual child participant? What safeguards are proposed to minimize these risks? When procedures involving greater than minimal risk to children are anticipated, are convincing scientific and ethical justifications given?
3. Is the inclusion of normal volunteers justified?
4. Do studies involving placebo controls place the child at increased risk by withholding from selected subjects potentially therapeutic research drugs or interventions?
5. When possible, have appropriate studies been conducted on animals and adults first? Will older children be enrolled before younger ones?
6. What is the age of majority in the state? Can a child consent to medical care for certain conditions and, if so, at what age? What legal limits are there on the right of parents to consent on behalf of their children?
7. Is permission of both parents necessary? Under what conditions may one of the parents be considered "not reasonably available"?
8. Will efforts be made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?
9. Are mechanisms in place to ensure that children are involved as research subjects in ways that do not undermine their dignity as young persons? Are provisions made that show respect for the developing rights of children, such as (a) obtaining their assent and, where appropriate, honoring their dissent; and (b) protecting their need for privacy and the confidentiality of information regarding them?
10. Do special problems call for the presence of a monitor or advocate during consent procedures?
11. Does the research design take into account special needs of adolescents, such as needs for counseling and confidentiality?
12. Might special problems arise concerning issues such as confidentiality and reporting in sensitive research about child abuse or sexual practices of teenagers?
13. If conditions present in children have implications for the health status of other family members (e.g., genetic risks or HIV infection), are appropriate mechanisms proposed for dealing with the larger family unit?
14. Should parents be required to be present during the conduct of the research? (Are proposed subjects to be very young? Are the procedures involved painful? Must subjects stay overnight in the hospital when they otherwise would not have to?)

The DOE Human Subjects Research Projects Database

A. Introduction

In the spring of 1994, the U.S. Department of Energy (DOE) made available a public database with information on all active human subjects projects funded by DOE, conducted in DOE facilities, or conducted by DOE personnel. This effort was part of Secretary of Energy Hazel O'Leary's "Openness Initiative" and the result of a commitment Secretary O'Leary made to Congress in early 1994.

The database allows easy access to information on current research involving human subjects funded by DOE at its national laboratories or at academic research institutions. The database also includes research involving human subjects funded by other agencies and conducted at DOE laboratories.

An example of the benefits to the public of DOE's research over the years has been the development of the entire field of nuclear medicine, which provides valuable diagnostic and therapeutic capabilities to treat diseases such as cancer. DOE is one of 16 Federal agencies supporting research involving humans. Both departmental and Federal-wide regulatory systems for the protection of human subjects are in place. The systems ensure that research meets or exceeds the highest standards of ethical conduct, including informed consent of the participants.

Research involving human subjects includes activities ranging from written questionnaires to actual experiments. Projects involving questionnaires, analysis of blood or urine samples, diagnostic medical exams, or gathering epidemiological data are considered to be research involving human subjects, primarily because personally identifiable data may be collected.

DOE funds research involving humans for a number of reasons. One of its legislative mandates is to develop new diagnostic and therapeutic applications in the area of nuclear medicine. An example is Brookhaven National Laboratory's development of new radiopharmaceuticals for detecting tumors. Another example is a study at the Memorial Sloan-Kettering Cancer Center to develop monoclonal antibodies labelled with a radioactive isotope, so-called "magic bullets," for detecting and treating cancer.

Other agencies also fund human subjects research at DOE laboratories because of the laboratories' world-class facilities and expertise. Examples are a National Institutes of Health (NIH)-funded study at the Lawrence Berkeley Laboratory of the effects of exercise and diet on cholesterol levels and a Department of Justice/National Institute of Justice-funded study at the Sandia National Laboratories of a less-than-lethal "sticky foam" restraint system.

In addition, as part of its responsibility as an employer to ensure the health of its workforce, DOE has an agreement with the Department of Health and Human Services' Centers for Disease Control and Prevention to study workers at DOE facilities in the normal course of their jobs. By reviewing occupational histories and death certificates, researchers are able to track the health status and mortality of current or former contractor workers at DOE's weapons complex.

DOE will update the database annually. For this effort, each institution must report all research projects involving human subjects that were active during the Government fiscal year ending September 30 and that were funded by DOE, conducted in DOE facilities, or conducted by DOE personnel. Starting in 1995, each institution will be able to enter project and institution data directly into the database either on diskette or via Internet.

The database is to be used only for reporting information about active human subjects research projects (active during the reporting fiscal year). It is *not* to be used for submitting proposals or for approval of human subjects research.

A copy of the database form is available on the following pages. The cover sheet and accompanying instructions offer additional details on the project reporting process.

Confidential and Proprietary Information

Institutions should be sensitive to classified, confidential, or proprietary data when entering projects in the database. All information entered into the database will be made available to the public unless stated otherwise on the database form. It is recommended that data for projects that include confidential or proprietary information be reviewed by secondary parties [e.g., Cooperative Research and Development Agreement (CRADA) partners] before being entered into the database.

Withholding of Information From the Database

Information concerning possible patentable inventions in which the United States has an interest can be withheld from public disclosure for a reasonable period of time to allow for the filing of a patent application. This is permitted by 35 USC 205. An appropriate disclaimer for inclusion in the database, in lieu of disclosure of such information, would be—

> The objective of this project is to reduce to practice a (named) invention. Pursuant to 35 USC 205, technical information relating to this invention will not be released until a patent application has been filed.

However, parties other than the United States may own or have an interest in project information considered for inclusion in the database. Data produced under a CRADA would be the property of the party producing it; data produced under a nongovernment-funded Work-for-Others

agreement would be owned by the paying sponsor. Statutes other than 35 USC 205 could affect the disclosure or nondisclosure of such information. Because different governing contractual provisions affecting data ownership are used throughout the DOE complex, questions regarding ownership, disclosure, and the appropriate disclaimers to be used in specific cases of nondisclosure should be referred for guidance and/or resolution of Patent Counsel in the cognizant Operations Offices.

B. The FY 1994 Human Subjects Research Projects Database

Summary Information

Following are some statistics about the 175 studies included in the FY 1994 database:

- One hundred and six projects received DOE support, 70 at DOE laboratories and 36 at other institutions. An additional 69 projects at DOE laboratories were funded by other agencies, such as the National Institutes of Health (NIH).

- DOE funded approximately $46 million in projects involving human subjects. Of this amount, a little more than $20 million went to one project—a Radiation Effects Research Foundation study looking at the effects of radiation on survivors of the atomic bombs detonated in Hiroshima and Nagasaki in 1945. Other agencies funded an estimated $10 million in projects performed at DOE laboratories.

- The studies involved a total of about 725,000 individuals in the United States. Of these, 360,000 were part of two epidemiological studies of current and former DOE and DOE contractor employees. Another 321,000 were involved in a questionnaire study of runners and their health. One of the studies was a joint U.S.–Japanese long-term followup study of approximately 138,000 survivors of the atom bomb attacks on Nagasaki and Hiroshima.

- In all of the projects involving radiation, the radiation was used as a tracer to facilitate imaging or other studies or for diagnostic or therapeutic reasons. DOE does not support any projects in which the effect of radiation upon humans per se is the object of study.

The FY 1994 human subjects research projects database continues to be accessed on a regular basis by a large number of users. From October 1, 1994, through March 31, 1995, a total of 10,658 queries were recorded. Requests came in from 45 different countries at an average of 56 queries per day.

Accessing the FY 1994 Database Through the Internet

Following are instructions on how to access the FY 1994 DOE Human Subjects Research Projects Database:

The FY 1994 DOE Human Subjects Research Projects Database is available to the public via the two most popular methods used to retrieve information across the Internet—Gopher and the World Wide Web (WWW). Access by WWW provides a more sophisticated and powerful interface to the database and thus may be preferable to Gopher access.

For anyone who already has access to Gopher client software, the database may be reached at the Johns Hopkins University Computational Biology Gopher server by pointing a Gopher client at gopher.gdb.org and selecting:

→ NIH, NSF, DOE, and Other Funding Agencies/

→ DOE—Department of Energy/

→ The DOE Subjects Database/

For anyone who already has access to WWW client software, the database may be reached at the Johns Hopkins University BioInformatics WWW server. The URL for that server is: http://www.gdb.org/hopkins.html. The database can also be accessed through DOE's Office of Health and Environmental Research WWW homepage. The URL for that server is: http://www.gdb.org/HTB/htb.html.

Gopher client software is available for X-Windows, Unix workstations, Vax/VMS, Macintoshes, and Intel-based PCs running Windows. The software and information about installing and using the software may be obtained by anonymous ftp (file transfer protocol) from boombox.micro.umn.edu in the pub/gopher directory.

NCSA Mosaic is an excellent WWW client and is available for X-Windows, Macintoshes, and Intel-based PCs running Windows. Any or all of these can be obtained by anonymous file transfer protocol (ftp) from ftp.ncsa.uiuc.edu in the /Web directory (ftp://ftp.ncsa.uiuc.edu/Web).

Lynx is a good WWW client for Unix and Vax/VMS systems for those who do not have access to network-connected systems with graphical user interfaces. Lynx is available by anonymous ftp from ftp2.cc.ukans.edu in the /pub/lynx directory (ftp://ftp2.cc.ukans.edu/pub/lynx).

Johns Hopkins University offers a dial-up connection to Gopher and WWW client systems. This can be reached by using a modem to dial (410) 614-2665. Modem settings are as follows: 8 bits, no parity, 1 stop. For a Gopher client, login as gopher. For a WWW client (Lynx) login as www.

C. The FY 1995 Human Subjects Research Projects Database

FY 1995 Database Update

The Office of Health and Environmental Research at DOE has revised the FY 1994 human subjects research projects database and is preparing for the FY 1995 update.

Reference Material Included in This Chapter

- FY 1995 Database Questionnaire (Figure 12a).
- FY 1995 Database Questionnaire Instructions (Figure 12b).

Following are some of the new features to be available in the 1995 database:

- The database questionnaire will be available on diskette and on the Internet.
- The instruction sheet will include sample responses, definitions, and directions for accessing and using the project summary form electronically.
- Fields have been added to collect information on protocols or subprojects that are linked to projects.
- Some fields allow respondents to select items from lists to facilitate the reporting process and to increase consistency in responses.

FY 1995 Database Questionnaire and Instructions

Following are the database questionnaire and instructions (Figures 12a and 12b) that will be used to facilitate input for the FY 1995 database update.

Figure 12a. FY 1995 Database Questionnaire

DATABASE QUESTIONNAIRE

U.S. Department of Energy
Human Subjects Research

Protecting Human Subjects | U.S. Department of Energy | Office of Health and Environmental Research

POLICY

Research activities that involve human subjects and that are funded by the U.S. Department of Energy (DOE), conducted in DOE facilities, or conducted by DOE personnel must be reviewed and approved or exempted from review in accord with Title 10, Code of Federal Regulations, Part 745. Failure to comply with these regulations may prevent DOE from authorizing or funding an activity, or may lead the Department to suspend or terminate the project.

SUBMISSION

Information on human research projects must be submitted on diskette [included] *and* in hard copy to DOE by **5:00 p.m. EST, November 1, 1995.** Note that direct entry of project data through the Internet may be available in the near future. However, until you are notified of the availability of this option, you should plan on submitting your data on the diskettes provided. The address for the questionnaire on the Internet will be http://www.eml.doe.gov.

Send the signed printout of your input and diskettes to—

U.S. Department of Energy
Environmental Measurements Laboratory
Protection of Human Subjects
376 Hudson Street
New York, NY 10014

This form is to be used only for providing DOE with information about active research projects (active during fiscal year 1995) that involve the use of human subjects. It is not to be used for submitting proposals or for approval of human subjects research.

NOTE: Project information in the database will be made available to the public.

DIRECTIONS

This form should be used as a guide for entering project information into the database. This form can be used for reporting site and project information, if the database via diskettes or the Internet is inaccessible. This form has 4 sections:

A. Site Summary
B. Project Identification
C. Funding Information
D. Information on Use of Human Subjects

Section A collects information on the institution where the projects are performed. Sections B, C, and D collect project-specific information. Complete section A once for your facility. Complete sections B, C, and D *for each research project* you are reporting. Complete section D for each protocol/subproject associated with a project.

All research activity using human subjects that was funded by DOE, performed by DOE personnel, or conducted at DOE facilities at any time during the 1995 fiscal year (October 1, 1994–September 30, 1995) must be included in the database.

Refer to the accompanying instructions for clarification on specific items in the summary form. For additional guidance, contact—

Dr. Lambros Kromidas
Environmental Measurements Laboratory (EML)
Tel: 212-620-3622
Fax: 212-620-3600
E-mail: kromidas@eml.doe.gov

Questions regarding the database and Internet questionnaire should be addressed to—

Camille Marinetti (EML)
Tel: 212-620-3272
Fax: 212-620-3600
E-mail: cgm@eml.doe.gov

U.S. DOE Human Subjects Database 1

Figure 12a. FY 1995 Database Questionnaire *(continued)*

A. Site Summary

1. SITE NAME AND SITE CODE:

_____ _____
Site Name Site Code

2. NAME OF PERSON PROVIDING DATA (FOR DOE USE ONLY):

Mr. ☐
Ms. ☐
Dr. ☐

Name: _____ _____ _____
First MI Last

Telephone: (____) _____ – _____ Ext: _____ Fax: (____) _____ – _____

E-mail Address: _____

3. PUBLIC INFORMATION CONTACT:

Mr. ☐
Ms. ☐
Dr. ☐

Name: _____ _____ _____
First MI Last

Address: _____

City: _____ State: _____ Zip: _____ Country: _____

Telephone: (____) _____ – _____ Ext: _____ Fax: (____) _____ – _____

E-mail Address: _____

4. INSTITUTIONAL REVIEW BOARD (IRB):

a. Did the project(s) reported here obtain approval from an IRB located at your site?

☐ Yes ☐ No

b. If No, institution whose IRB approved the project(s):

_____

c. Does the IRB that approved your project(s) operate under a Multiple Project Assurance (MPA) recognized by DOE or by the Department of Health and Human Services?

☐ Yes ☐ No

d. If Yes, enter the MPA number of the IRB: _____

5. HOW MANY HUMAN SUBJECT PROJECTS ARE YOU REPORTING?

Number of projects: _____

You must fill out Sections B, C, and D for EACH project you are reporting. Make copies of these sections as needed.

SIGNATURE OF AUTHORIZED OFFICIAL(S):

I certify that the information attached is correct.

Name: _____ Title: _____

Signature: _____ Date: _____

Name: _____ Title: _____

Signature: _____ Date: _____

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Figure 12a. FY 1995 Database Questionnaire *(continued)*

B. Project Identification

Project I.D.: _____

Note: For questions or concerns regarding proprietary data, see Section B of the instructions or contact your institution's human subjects research point of contact.

6. PROJECT IDENTIFIER (Do not include site code or fiscal year.):

_____

7. PROJECT TITLE:

_____

8. PRINCIPAL INVESTIGATOR (PI):

Mr. ☐
Ms. ☐
Dr. ☐

Name: _____ (First) _____ (MI) _____ (Last)

9. PI'S INSTITUTION:

_____

10. PROJECT START YEAR:

a. Is this a new project? (Did it begin during the 1995 fiscal year?) ☐ Yes ☐ No

b. If No, year project started: _____

C. Funding Information

11. ZERO FUNDING:

a. Did this project have funding during fiscal year 1995 (October 1, 1994 – September 30, 1995)?

☐ Yes ☐ No

b. Did this project involve the use of human subjects during fiscal year 1995?

☐ Yes ☐ No

c. If no to a and/or b, please explain: _____

12. TYPE OF SOURCE:

Mark all categories from which funding for this project was received:

☐ DOE funding source(s) ☐ Other Federal agency source(s) . ☐ Non-Federal source(s)

U.S. DOE Human Subjects Database 3

Figure 12a. FY 1995 Database Questionnaire *(continued)*

Project I.D.: _____

DOE FUNDING (cont'd)

Possible Funding Sources:

DOE Funding Sources:

Civilian Radioactive Waste Management
Defense Programs
Energy Efficiency and Renewable Energy
Energy Information Administration
Energy Research (ER)
  Office of Health and Environmental Research (OHER)
Environmental Management
Environment, Safety and Health (EH)
  Office of Epidemiology and Health Surveillance
  Office of Occupational Medicine
Fossil Energy
Intelligence and National Security
Nuclear Energy
Other
  Indirect laboratory funds
  Laboratory-Directed Research Development (LDRD) Funds
  Operations Office
  Other (*Please specify*)

Other Federal Agency Sources:

Department of Defense,
  (Air Force, Army, Navy, other)
Department of Health and Human Services
  National Institutes of Health (*Specify division.*)
  National Institute of Occupational Safety and Health (NIOSH)
  Other parts of Health and Human Services (*Specify source.*)
Department of Justice
Department of Transportation
Environmental Protection Agency
National Aeronautics and Space Administration
Nuclear Regulatory Commission
U.S. Postal Service
U.S. Secret Service
Other (*Specify source(s) or state obligation to withhold proprietary or classified information.*)

Note: If your project has more than two funding sources, copy this page and fill it out accordingly.

13. SOURCE INFORMATION:

a. Source of funding: _____ *(Refer to list above.)*
b. Amount of funds received from this source that were associated with the use of human subjects for fiscal year 1995 (October 1, 1994 – September 30, 1995):
_____
c. Is this amount estimated? ☐ Yes ☐ No
d. Comments: _____
_____
_____

a. Additional source of funding: _____ *(Refer to list above.)*
b. Amount of funds received from this source that were associated with the use of human subjects for fiscal year 1995 (October 1, 1994 – September 30, 1995):
_____
c. Is this amount estimated? ☐ Yes ☐ No
d. Comments: _____
_____
_____

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Figure 12a. FY 1995 Database Questionnaire *(continued)*

Project I.D.: _____

D. Information on Use of Human Subjects

Note: This section should be filled out once for a project and multiple times for the number of protocols/subprojects associated with a project.

14. PROTOCOLS/SUBPROJECTS:

a. Does this project involve the use of protocols/subprojects that are individually approved by the IRB?

☐ Yes ☐ No (*Go to question 16.*)

b. If Yes, how many protocols/subprojects are associated with this project? _____

Fill out questions 15-19 for EACH protocol/subproject associated with this project. Make copies of this section as needed.

15. PROTOCOL/SUBPROJECT IDENTIFIER/NUMBER:

_____

16. IRB REVIEW:

a. Type of Review *(Select one)*: ☐ Full Board ☐ Expedited

b. Date of Most Recent IRB Approval (*Use this format: MM/DD/YY*): _____

c. IRB Approval Number (if any): _____

17. NUMBER OF HUMAN SUBJECTS:

For new projects, enter the total number of human subjects who have participated in this project (protocol/subproject) since the initial IRB approval (certification).

For continuing projects, enter the total number of human subjects who participated in this project (protocol/subproject) during the year that preceded the last IRB approval (recertification). For example, if the last IRB approval was given on March 1, 1995, enter the number of human subjects that participated in this project between March 1, 1994, and March 1, 1995.

_____

18. TYPE OF HUMAN SUBJECTS INVOLVEMENT (Mark all that apply and answer related questions.):

Yes	No	
		a. Ionizing Radiation and Radioactive Substances:
☐	☐	1. *External* use of ionizing radiation on human subjects.
		If Yes, ☐ For clinical research?
		☐ For diagnostic research?
		☐ For therapeutic research?
		☐ Other. Explain: _____
☐	☐	2. *Internal* administration of radioactive substances to human subjects.
		If Yes, ☐ For clinical research?
		☐ For diagnostic research?
		☐ For therapeutic research?
		☐ Other. Explain: _____

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Figure 12a. FY 1995 Database Questionnaire *(continued)*

Project I.D.: _____

TYPE OF HUMAN SUBJECTS INVOLVEMENT (cont'd) (Mark all that apply and answer related questions.):

Yes No

b. Chemical Substances:

☐ ☐ 1. *External* use of chemical substances (solid, liquid, or gas) on human subjects.

If Yes,
- ☐ For clinical research?
- ☐ For diagnostic research?
- ☐ For therapeutic research?
- ☐ Other. Explain: _____

☐ ☐ 2. *Internal* use of chemical substances (solid, liquid, or gas) on human subjects.

If Yes,
- ☐ For clinical research?
- ☐ For diagnostic research?
- ☐ For therapeutic research?
- ☐ Other. Explain: _____

c. Collection of Bodily Materials:

☐ ☐ Collection of *personally identifiable* bodily materials (e.g., blood or blood products, urine, cells, tissue, teeth, organs, excretia or other waste materials).

If Yes,
- ☐ Does this project use cells cultured in a laboratory?
- ☐ Are bodily materials collected from subjects specifically for this project?
- ☐ Are existing specimens or samples of bodily material used that were collected for another purpose?

d. Questionnaires, Surveys, Epidemiological Studies:

☐ ☐ Use of personally identifiable data from questionnaires, surveys, or epidemiological studies.

If Yes,
- ☐ Are data collected from subjects (e.g., through interaction, observation) specifically for this project?
- ☐ Does the project use existing data that were collected for other purposes or projects?

e. Instrument/Device/Product Testing or Man-Machine Studies:

☐ ☐ Use of human beings to develop/test instruments, materials, devices, objects, and the like or to investigate "man-machine interface."

Figure 12a. FY 1995 Database Questionnaire *(continued)*

Project I.D.: _____

TYPE OF HUMAN SUBJECTS INVOLVEMENT (cont'd) (Mark all that apply and answer related questions.):

Yes No **f. Environmental/Human Habitat Studies:**

☐ ☐ Use of human beings for environmental studies (e.g., weatherization, energy-efficiency, lighting studies).

g. Other:

☐ ☐ Explain any other types of human subjects involvement.

_____
_____
_____
_____
_____

19. ADDITIONAL REQUIRED INFORMATION (ABSTRACT) (Up to 750 words in total—use additional paper, if necessary.)

Your response should include the following elements:

a. Objectives.

b. Methodology.

c. Ionizing Radiation, Radioactive Substances, or Chemical Substances. List any chemical or radioactive substances or ionizing radiation to which *human subjects* are exposed.

d. Involvement of Human Subjects.

1. Describe the procedures involving human subjects. If the project involves cell cultures, reproductive studies, or genetic engineering, include a description of these procedures.

2. Explain the risks, if any, to which human subjects are exposed.

_____
_____
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Figure 12b. FY 1995 Database Questionnaire Instructions

Human Subjects Research Questionnaire Instructions

Protecting Human Subjects

U.S. Department of Energy (DOE)
Office of Health and Environmental Research

Important: Project summaries will become part of a database that is open to the public.

A. Site Summary

1. Site Name and Site Code:

Name the institution—e.g., laboratory, university, company, research institute, hospital—responsible for this research project.

Enter a site code for your institution. Your site code is the standard abbreviation for your institution. Following are some examples:

Institution	Site Code
Sandia National Laboratories	SNL
Los Alamos National Laboratory	LANL
University of California at San Francisco	UCSF
Idaho National Engineering Laboratory	INEL

DOE will eventually attach your site code to the project identifiers for each of the projects you report.

2. Name of Person Providing Data (For DOE use only).

Provide the name, telephone number, fax number, and e-mail address, if any, of the person responsible for the accuracy of the information provided—the person who would respond if DOE Headquarters has questions regarding data submitted. At DOE facilities, this person is normally the Human Subjects Coordinator. (The person named here is not necessarily the person actually entering data into this form.) **Note:** This item of information will not be part of the public database.

3. Public Information Contact.

Give the name, address, telephone number, fax number, and e-mail address, if any, of the office or individual that should handle any inquiries from the public about this project. Investigators at non-DOE facilities may choose either to list themselves as points of contact or, alternatively, to identify a public information office or comparable office to handle initial inquiries from the public.

4. Institutional Review Board (IRB).

Research projects that involve use of human subjects must be reviewed and approved (or exempted from review) by an IRB. The IRB is responsible for assuring compliance with Title 10, Code of Federal Regulations, Part 745 and protecting the rights and welfare of human subjects who participate in research.

Continued—

Figure 12b. FY 1995 Database Instructions *(continued)*

4. Institutional Review Board (IRB) (continued).
Once the IRB has approved a project, work with human subjects may begin *provided* the institution has a Multiple Project Assurance (MPA) recognized by DOE or by the Department of Health and Human Services (DHHS). Every human research project must be assured under an MPA or an SPA with DOE or DHHS.

a. Indicate whether or not the IRB that approved the projects that you are reporting is located at your site/institution.

b. If the IRB that approved the projects that you are reporting is not located at your site/institution, enter the name of the institution whose IRB approved the project(s).

c. Indicate whether the institution of the IRB that approved your projects holds a Multiple Project Assurance (MPA) recognized by DOE or the Department of Health and Human Services (DHHS).

d. If the IRB that approved the projects that you are reporting holds an MPA recognized by DOE or DHHS, enter the MPA number.

5. How Many Human Subject Projects Are You Reporting?
Enter the number of projects you are reporting. This question will be used for quality assurance purposes. The response to this question will allow DOE headquarters to verify that it has received all reportable projects from your institution.

B. Project Identification

Special Note—Proprietary Information. The following statement was prepared by DOE's General Counsel's office regarding the withholding of proprietary information from the DOE Human Subjects Research Database:

Information concerning possible patentable inventions in which the United States has an interest can be withheld from public disclosure for a reasonable period of time to allow for the filing of a patent application. This is permitted by 35 USC 205. An appropriate disclaimer for inclusion in the database, in lieu of disclosure of such information would be:

> The objective of this project is to reduce to practice a (named) invention. Pursuant to 35 USC 205, technical information relating to this invention will not be released until a patent application has been filed.

Parties other than the United States may own or have an interest in project information considered for inclusion in the database, however. Data produced under a Cooperative Research and Development Agreement (CRADA) would be the property of the party producing it; data produced under a non-government-funded work-for-others agreement would be owned by the paying sponsor. Statutes other than 35 USC 205 could affect the disclosure or non-disclosure of such information. Because different governing contractual provisions affecting data ownership are used throughout the DOE complex, questions regarding ownership, disclosure and the appropriate disclaimers to be used in specific cases of nondisclosure should be referred for guidance and/or resolution to Patent Counsel in the Operations Offices.

Continued—

Figure 12b. FY 1995 Database Instructions *(continued)*

6. Project Identifier.
Each project must have a unique identification number that does not change over the life of the project.

The project identifier is assigned in nearly all cases by the Institutional Review Board (IRB) that approves the use of human subjects. For projects conducted at DOE facilities, DOE will attach the site code specified in question #1 and the fiscal year (FY) when the project was first approved by the IRB as a prefix to the identifier.

Projects at institutions that are not DOE facilities may use DOE grant/contract numbers as identifiers if the IRB does not provide a unique, unchanging project number. DOE will also add the site code specified in question #1 and the fiscal year when the project was first approved by the IRB as a prefix to project identifiers of non-DOE facilities.

For example, a typical project identifier may be—"EML-95/101-321." DOE will attach the prefix (EML-95/). The institution must provide the unique project identifier (101-321). The identifier will appear on each printed page of the data summary.

7. Project Title.
For continuing projects, make sure that the title matches the title reported last year unless there are substantive reasons for any differences. If the project does have a new title, enter the former title in parentheses after the new title. For example, ("Formerly, . . .").

8. Principal Investigator (PI).
Enter the name of the principal investigator for the project you are reporting. List no more than one principal investigator. If more than one senior investigator heads the project, select the person who should be the point of contact for answering any questions from DOE about use of human subjects.

9. PI's Institution.
The name of the institution entered for #1 will automatically appear here. If the principal investigator is located at a different institution, enter that institution's name here.

10. Project Start Year.

a. Indicate whether the project you are reporting is a new project (began in Fiscal Year 1995—October 1, 1994 through September 30, 1995).

b. If the project you are reporting is not a new project, enter the year when the project actually started.

Continued—

Figure 12b. FY 1995 Database Instructions *(continued)*

C. Funding Information

11. Zero Funding.

This year, all human research projects (funded or not) that have received IRB approval will be included in the database and should be reported here.

In the past, human subjects research projects were included in the database only if they had obtained funding. Exceptions to this rule were projects that actively used human subjects but had no funding. Examples included unfunded thesis projects, projects whose results were still being analyzed and reported even though funding had ceased, and followup studies that involve medical examinations every several years, but not in the year being reported.

Provide the following information for your project:

a. Indicate whether the project you are reporting had funding during the 1995 fiscal year (October 1, 1994–September 30, 1995).

b. Indicate whether the project you are reporting involved the use of human subjects during the 1995 fiscal year (October 1, 1994–September 30, 1995).

c. If your response to 11a and/or b is "no," please provide an explanation. For example—project received IRB approval, but funding was not obtained; unfunded thesis project; project's results are still being analyzed and reported even though funding has ceased; or project is a followup study that involves medical examinations every several years, but not in the year being reported.

12. Type of Source.

Mark all categories—DOE, other Federal, or non-Federal—from which funding for this project was received.

13. Source Information.

a. Select the name of the department or office from the list provided that provided funding for this project. Identify all sources of funding. Note that, in addition to DOE, the list includes other Federal sources and also sources outside the Federal Government.

If a project is funded through a *subcontract*, indicate the immediate source of funding. For example, if a DOE laboratory has a subcontract from a local hospital district to perform work for a grant that the hospital has obtained from the National Institutes of Health, the hospital district should be identified as the funding source.

b. *Report only funding associated with the use of human subjects.* Enter total funding from each funding source for fiscal year 1995 (October 1, 1994–September 30, 1995) for all tasks or portions of the project that involved use of human subjects (not the full funding for the entire project). In the funding you report, include both direct charges (labor and other) and indirect costs (e.g., fringe and overhead), plus any fee or profit (if applicable).

Important: Report only funding associated with use of human subjects. In some large projects, for example, only a few tasks involve working with human subjects or samples. In other cases, human subjects may be involved only at the end of a project, to test the device or materials developed in the course of the project.

Continued—

Figure 12b. FY 1995 Database Instructions *(continued)*

17. Number of Human Subjects.
For new projects, enter the total number of human subjects who have participated in this project (protocol/subproject) since the initial IRB approval (certification).

For continuing projects, enter the total number of human subjects who participated in this project (protocol/subproject) during the year that preceded the last IRB approval (re-certification). For example, if the last IRB approval was given on March 1, 1995, enter the number of human subjects that participated in this project between March 1, 1994, and March 1, 1995.

18. Type of Human Subjects Involvement.
Mark all categories that apply to your project and answer related questions.

Important: Report use of *ionizing* radiation, radioactive substances, or chemical substances only if these are administered, externally or internally, to human subjects (in vivo). *Do NOT report in vitro use of radiation or radioactive/chemical substances.*

19. Additional Required Information (Abstract).
Include in your response, details on any of the types of human subjects involvement categories that you selected in question #18. Your response should contain the following elements. (Note that this information [abstract] must not exceed 750 words.)

a. **Objectives.** This section should indicate potential benefits of this research, to society or to the individual human subjects.

b. **Methodology.**

c. **Ionizing Radiation, Radioactive Substances, or Chemical Substances.** Note that this item deals only with *ionizing radiation or substances to which human subjects are exposed.* If human tissue is exposed to radioactive substances in the laboratory, for example, this exposure should *not* be reported here. If human beings are exposed to ionizing radiation or radioactive substances—internal or external—however, this exposure *should* be reported here.

d. **Involvement of Human Subjects.** Several points are important here:

- The summary should distinguish clearly between any procedures that directly involve human beings (*in vivo*) and any that apply only to human samples or specimens following collection (*in vitro*).
- It should likewise distinguish between samples or data collected specifically for this project/protocol/subproject, e.g., through interaction with or observation of human subjects in the course of the project, and samples or data collected for other purposes.
- The summary should clearly identify any procedures associated with in-vitro fertilization, cell culture, or genetic engineering.
- Procedures to protect privacy and confidentiality should be explained.
- Finally, note that risk includes a variety of possible types of harm—not only physical injury or disease, but potential inconvenience, embarrassment, loss of privacy, and economic loss, among others.

Continued—

Figure 12b. FY 1995 Database Instructions *(continued)*

Signature of Authorized Official(s).
At *DOE facilities*, the Human Subjects Coordinator must sign the paper printout of the complete institution report submitted to DOE. Another institutional official such as the IRB Chair may also sign the complete institution report. At other institutions, the project summaries and site information may be signed by the IRB Chair, by the head of the department or division where the principal investigator is located, or by the funding contact at DOE.

Performance Review and Educational Outreach

A. Introduction

This chapter provides information on the review of human subjects research within the Federal Government and on U.S. Department of Energy (DOE) educational materials.

The following section in this chapter describes DOE's proposed system for ensuring that DOE laboratories and other facilities are conducting DOE-supported human subjects research in accordance with the ethical and procedural standards described in 10 CFR 745 and DOE Order 1300.3. The proposed system is not considered to be an audit, but rather a performance review and an educational system to assist research institutions and DOE operations and program offices in improving processes for the protection of human subjects involved in research funded by DOE, performed by DOE personnel, or conducted in DOE-owned facilities. This system is scheduled to begin in 1996.

Reference Materials Included in This Chapter

- Specific Items for Review or Verification During a Protection of Human Subjects Performance Review (Figure 13a).
- HERAC Response Checklist (Figure 13b).
- U.S. Food and Drug Administration—A Suggested Self-Evaluation Guide (Figure 13c).
- NIH, Office for Protection from Research Risks—Compliance Oversight Procedures (Figure 13d).

Also included in this chapter are checklists to assist reviewers in conducting a comprehensive evaluation of activities dealing with protection of human subjects, whether in DOE laboratories, operations offices, or program offices.

Information on National Institutes of Health (NIH) and U.S. Food and Drug Administration (FDA) audit processes is found toward the end of this chapter (Figures 13c and 13d).

B. DOE's Performance Review System

Purpose

On May 27, 1994, a subcommittee of the Health and Environmental Research Advisory Committee (HERAC) in DOE's Office of Health and Environmental Research (OHER) submitted a report to Dr. Martha Krebs, Director, Office of Energy Research, on protection of human subjects at DOE facilities. In its report, the subcommittee recommended that DOE implement regular site visits to review the performance of each IRB. This recommendation was accepted and plans for the site visits (performance reviews) were developed and described in the official response to the HERAC subcommittee report submitted to Congress. The purpose of DOE's performance review system is to ensure that the ethical considerations described in 10 CFR 745 and DOE Order 1300.3 are being addressed and to suggest where improvements can be made. Following is a description of the performance review system scheduled to begin in 1996.

Composition of Review Teams

For DOE laboratories, it is recommended that review teams consist of five members such as an ethicist, a physician, an attorney, an individual knowledgeable about special research and procedures under review—possibly a scientist or a member of another institution's institutional review board (IRB)—and a representative of OHER.

For DOE's operations office procedures and practices, it is recommended that two members of DOE's ad hoc Human Subjects Working Group and one outsider serve as the evaluation team, whereas review of DOE's headquarter program offices could include one individual from operations offices, one individual from another program office, and one DOE Human Subjects Working Group member.

Options and Mechanisms

Site Visit

It is anticipated that OHER will be responsible for selecting an appropriately constituted team and appointing a team leader. OHER will also be responsible for notifying laboratory management of the visit in advance. Notification should include the scope of the review (an agenda), identification of personnel at the laboratory who should meet with the review team, and the types of documents to be reviewed. The review team will spend as much time as necessary conducting the review and presenting findings and recommendations at a meeting with laboratory management and the chairperson of the institution's IRB.

Alternatives to Site Visit

OHER may, at its discretion, use any or all of several alternatives to a site visit. It may use written questions and answers such as those found in the Health and Environmental Research and Advisory Committee (HERAC) response checklist, conduct selected interviews with responsible members of management or an institution's IRB, or conduct a review of an institution's implementation plan for the protection of human subjects. It may also use the

HERAC self-assessment table or equivalent for program or field office reviews. The two noted checklists are included in this chapter.

Frequency of Reviews

It is proposed that a routine evaluation be conducted once every 3 years, whereas nonroutine reviews will depend upon special circumstances such as reports of unsatisfactory performance or serious adverse events.

Use and Distribution of the Performance Evaluation

The performance evaluation should be used for developing educational recommendations for management concerning areas or processes in need of improvement. To provide maximum help, the evaluation should include areas of concern as well as recommendations for improvement. The evaluation should be distributed to laboratory management, the cognizant area office (if appropriate), operations office, and OHER. If the institutional assurance is filed with an agency other than DOE, courtesy copies may be distributed to the other Federal agencies or departments that have supported or conducted research reviewed during the site visit.

Key Points for Reviewers

At both the opening and the closing of the site visit, the review team should emphasize the educational value of the process and the desire for performance improvement. Prior to the visit, the team should identify and evaluate relevant reviews previously conducted by DOE or another agency such as FDA, and it should develop and execute a review plan and provide a followup formal report with the evaluation and recommendations.

Followup Report

The review team should prepare and review the followup report, which should be submitted within 3 to 4 weeks after the review has been conducted. The review team should request that a corrective action plan be provided by the reviewed organization within 3 to 4 weeks of receipt of the formal review report; this may be waived if review findings are insignificant. OHER should work through management channels to ensure that the corrective action plan, if prepared, has been effectively implemented over a reasonable period of time. It is essential that confidentiality of all records reviewed in the conduct of the evaluation be maintained.

C. DOE Checklists/Self-Evaluations

The following two checklists (Figures 13a and 13b) should be used by DOE facilities as self-evaluations or in preparation for a DOE performance review. DOE reviewers will use these checklists during a review to ensure a comprehensive assessment of activities involving human subjects.

Figure 13a. Specific Items for Review or Verification During a Protection of Human Subjects Performance Review

Institution	Institution Management	Institutional Review Board (IRB)	Principal Investigator (PI)
Procedures/ Policies/ Authorizations	• Mechanism to ensure proposals/ applications for research involving human subjects are identified. • Written procedures for management review and approval of protocols and consent forms. • Current institutional document delegating authority to IRB. • Provisions for continuing guidance and education to researchers on matters pertaining to protection of human subjects.	• IRB operational procedures.	• Institutional guidelines for PIs proposing research on human subjects.
Approvals/ Consent	• Original, signed consent form.	• Approval from IRBs of other participating institutions in collaborative research. • Approval document for studies involving human subjects.	• Approval from authorized institutional official. • Comments/approval from co-investigators. • Requests for IRB approvals from foreign collaborators. • IRB approval for any protocol amendments, consent form changes, or change in scope of work. • Annual IRB approval for continuation of human subjects projects. • Valid consent form from each subject.
Records/Files/ Correspondence	• Central archive for retention of all written materials on studies involving human subjects. • Separate files for each protocol/subproject within a large project (IRB number for each protocol). • Copy of assurances, project data summaries, IRB certification, approved project/protocols, and consent forms. • Copy of IRB concurrence letter and abstract from PI.	• Documentation of receipt of protocols, consent forms, and subsequent actions. • PI recommendation for exemption status with basis and project abstract. • Statements of required project/ protocol or consent form changes requested by IRB members. • Record of IRB transactions, correspondence, and reports.	• Written detailed project/protocol and associated consent forms. • Letter from IRB stating actions on protocol, consent forms, and other IRB actions.
Reports/Status/ Notifications	• Annual listings of status of all research projects involving human subjects. • Annual report from PI on status of study. • Notifications from PI of any injuries to subjects, unanticipated risks, or adverse events. • Any FDA reports of IRB audits.	• Annual report from PI on status of study. • Notifications from PI of any injuries to subjects, unanticipated risks, or adverse events.	• Any notifications to IRB/institution management of any injuries to subjects, unanticipated risks, or adverse events.
Resources	• Allocation of sufficient resources.		

Continued—

Figure 13a. Specific Items for Review or Verification During a Protection of Human Subjects Performance Review *(continued)*

DOE	OHER (ER-70)	Program Secretarial Officer (PSO)	DOE Field Office	DOE Contracting Officer
Procedures/ Policies/ Authorizations	• Guidance to be followed for obtaining approval for human subjects research. • Each institution's current written delegation of authority granting IRB necessary powers.	• Mechanisms ensuring proposals/applications for research involving human subjects are identified.		
Approvals/ Consent	• Approval letters for all human subjects assurances. • Recommendations for approval of compliance from field office for field office-delegated work.		• OHER (ER-70) approval of compliance with 10 CFR 745.	• OHER (ER-70) approval of compliance with 10 CFR 745.
Records/Files/ Correspondence	• Copy of assurances, IRB certifications, approved IRB memberships, initial approved protocols, and consent forms.	• Determination of compliance with 10 CFR 745 from ER-70. • Verification of acceptability of IRB project certification.	• Properly executed certification of IRB review, approval, or declaration of exemption. • Copies of IRB-approved protocols and consent forms. • Assurance documents or references to existing approved assurances.	• Complete assurance, certification, OHER (ER-70) approval document prior to initiation of research involving human subjects.
Reports/Status/ Notifications	• Documentation of review, evaluation, or action on reported adverse events. • Copies of FDA audit reports from laboratories.			
Resources	• Allocation of sufficient resources.		• Allocation of sufficient resources.	

Figure 13b. HERAC Response Checklist

On May 27, 1994, HERAC of OHER submitted a report to the Office of Energy Research on the protection of human subjects at DOE facilities. Included in the report were several recommendations to IRBs. The DOE Human Subjects Working Group combined most of the recommendations to the IRBs into the following survey table. The Working Group has included additional recommendations, some of which are directed to operations offices and laboratories. This table should be used by DOE operations offices and laboratories as a self-assessment in evaluating their performance in accord with Federal regulations on the protection of human subjects and with HERAC report recommendations.

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
1. IRB Composition				
Nonaffiliated and nonscientist members present and participating as defined in the regulations.	YES	NO		
Attendance at the IRB meetings by a representative sufficiently knowledgeable of the vulnerable population.	YES	NO		
2. Consent Process				
IRB assures procedure to evaluate subject's capacity to consent and its possible diminution over time.	YES	NO		
Legal representative or acceptable surrogate provides consent in cases where subject lacks capacity to consent.	YES	NO		
IRB annually reviews and dates each consent form whether or not modifications have been made.	YES	NO		
Essential information conveyed in the consent process is documented and is in a form easily understood by the subjects.	YES	NO		

Continued—

Figure 13b. HERAC Response Checklist *(continued)*

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
3. Expedited and Exempt Categories of Research				
IRB has a thorough understanding of the difference between expedited and exempt categories of research.	YES	NO		
4. Renewals				
IRB conducts a full and substantive review of project/protocol renewals.	YES	NO		
5. Collaborative/Cooperative Research Agreements				
IRB reviews the human subjects component of all collaborative research, CRADAs, and other cooperative agreements. Decisions of DOE-site IRB are binding on personnel of all collaborating parties, where a contractual agreement exists. Appropriate clauses imposing this requirement as a binding obligation on third-party participants will be included in the subject contractual agreements.	YES	NO		
6. IRB Minutes—				
Indicate committee member attendance at meetings.	YES	NO		
Describe actions taken by IRB on each project.	YES	NO		
Record the vote taken on actions by IRB, including number of members voting for, against, or abstaining.	YES	NO		
Document the basis for requiring changes in or disapproving research.	YES	NO		

Continued—

Figure 13b. HERAC Response Checklist *(continued)*

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
Summarize discussion of significant controversial issues and their resolution.	YES	NO		
Record the time that each meeting begins and ends.	YES	NO		
Identify any IRB member who, because of a conflict of interest, does not participate in a discussion or abstains from voting.	YES	NO		
Are taken by a non-voting member of the board or a secretary.	YES	NO		
7. IRB Files—				
Contain all documents required by the regulations and departmental policies, such as copies of all research proposals reviewed; scientific evaluations, if any, that accompany the proposals; approved sample consent documents; progress reports; and reports of injuries to subjects or other adverse events.	YES	NO		
Reflect all pertinent communications with principal investigators and include a dated copy of the most recently approved protocol and consent form, including information on whether or not modifications were requested.	YES	NO		
8. IRB Authority				
IRB has written delegation of authority, granting IRB all powers necessary to fulfill responsibilities, as set forth in 10 CFR Part 745.	YES	NO		

Continued—

Figure 13b. HERAC Response Checklist *(continued)*

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
Copy of the written delegation of authority is on file at DOE Headquarters.	YES	NO		
9. Audits				
Laboratory submits to headquarters (through the operations office) a copy of all FDA, NIH, and other audit reports together with the laboratory's written response. Per regulation requirements, adverse events are reported to the IRB, the funding agency, and DOE.	YES	NO		
10. Human Subjects Point of Contact				
Laboratory has indicated to DOE its current Office of Research Administration (ORA) point of contact, and this person is responsible for communications with the Headquarters Program Manager and Operations Office Coordinator.	YES	NO		
11. Sufficient Resources To Perform Human Subjects Responsibilities: Laboratories				
*IRB Administrator or ORA (Human Subjects Point of Contact)—at a minimum, a half-time person.	YES	NO		
*Half-time or adequate secretarial support.	YES	NO		
Dedicated space for records—file cabinets.	YES	NO		
Equipment—computers, printer, copy machine, etc.	YES	NO		
Data processing and programming support.	YES	NO		

*Dependent upon the level of activity at each site.

Continued—

Figure 13b. HERAC Response Checklist *(continued)*

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
Compensation for Human Subjects Committee members, if appropriate.	YES	NO		
Travel funds for IRB Administrator, ORA (Human Subjects Coordinator), and IRB chairperson to attend DOE human subjects meetings and professional meetings, as appropriate.	YES	NO		
For Working Group members, travel for attending at least two Human Subjects Working Group meetings per year.	YES	NO		
Funding for education and training for ORA, IRB chairperson, and laboratory staff, as needed.	YES	NO		
Time for responding to headquarters' requests (e.g., database updates, document review, Working Group meetings).	YES	NO		
12. Sufficient Resources To Perform Human Subjects Responsibilities: Operations Offices				
ORA (point of contact)—at a minimum, a half-time person*—adequately staffed to properly coordinate the administration of human subjects protection.	YES	NO		
Time for coordinating or performing training on site.	YES	NO		
Travel for at least one professional/ educational meeting per year.	YES	NO		

*Dependent upon the level of activity at each site.

Continued—

Figure 13b. HERAC Response Checklist *(continued)*

Recommendation	Is your facility *currently* operating in accordance with this recommendation? (Please circle yes or no.)		If your facility is not currently operating in accordance with this recommendation, please explain. Specify the date by which you expect your facility to be responsive.	What resources or materials does your facility need in order to respond?
For Working Group members, travel for attending at least two Human Subjects Working Group meetings per year.	YES	NO		
Time for responding to headquarters' requests (e.g., database updates, document review, Working Group meetings).	YES	NO		
Time and support for onsite education—making sure the site is in compliance, providing educational/ training sessions when necessary, and developing a team that would perform regular internal evaluations of human subject practices, policies, and processes.	YES	NO		

D. Compliance Investigations by Other Federal Agencies

FDA conducts routine audits of all laboratories subject to its regulations and has prepared a self-evaluation checklist to assist institutions in taking corrective action prior to formal audits. The Office for Protection from Research Risks (OPRR) does not conduct formal audits in the absence of evidence of noncompliance or reports of repeated serious adverse events. In the event that a DOE facility is audited by either FDA or OPRR, the facility is required to submit to DOE headquarters (ER-70) a copy of any reports, as well as followup and closure documents, regarding the audit. Both the NIH and the FDA audit processes are described in the following two documents (Figures 13c and 13d).

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards[1]

October 1, 1995

A SELF-EVALUATION CHECKLIST
FOR INSTITUTIONAL REVIEW BOARDS

The Food and Drug Administration (FDA) has regulations that govern human subject protection aspects of research on products regulated by the Agency. In addition, other federal agencies and departments and some States have regulations that govern human subject protection. Each institution should be familiar with the laws and regulations that apply to research conducted at the institution. This checklist was developed to help institutions evaluate procedures for the protection of human subjects of research.

Through its review of IRB activities, FDA has been impressed by the variety of procedural systems that have been developed to protect human subjects. At the same time, successful IRBs make use of written procedures that, in one way or another, cover a common core of topics. This checklist is an effort to present these topics in a systematic way. Some of the items are not covered by FDA regulations (e.g., policy regarding place and time of meeting) but may be appropriate to consider when comprehensive procedures are being developed. FDA does not expect institutions to develop procedural statements responding to each item in the list. Rather, the checklist should be used to identify procedures that may be needed to meet an institution's particular situation.

Once an institution establishes its IRB structure and procedures, those procedures should be followed. FDA inspections assess compliance on both the regulatory requirements as well as on the institution's own written procedures. The institutional procedures should reflect the current processes. Therefore, policies and procedures should be reviewed on a regular basis and updated as necessary. FDA believes that when good procedures are developed, written, and followed, the rights and welfare of the subjects of research are likely to be adequately protected.

Tips on checklist use:

Three "response" columns are provided—"Yes," "No," and "N/A." A "Yes" means that the institution has a policy/procedure and that it is current. A "No" may mean that a policy/procedure is lacking or needs to be updated. The "N/A" column indicates that a topic is not applicable or a procedure is not needed in the institution.

The columns may be completed by checking the appropriate box. Instead of a check-mark, some institutions record the date of issuance or revision date. Others have found it useful to record the policy/procedure number on the form. Any "No" responses indicate a need to write/revise policies and/or procedures.

References to the FDA regulations are given for additional guidance on requirements.

Continued—

[1]Food and Drug Administration Information Sheets for Institutional Review Boards and Clinical Investigators, Appendix G.

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
I. THE INSTITUTIONAL AUTHORITY UNDER WHICH THE IRB IS ESTABLISHED AND EMPOWERED.			
II. THE DEFINITION OF THE PURPOSE OF THE IRB, i.e., THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH.[1]			
III. THE PRINCIPLES WHICH GOVERN THE IRB IN ASSURING THAT THE RIGHTS AND WELFARE OF SUBJECTS ARE PROTECTED.			
IV. THE AUTHORITY OF THE IRB.			
A. The scope of authority is defined, i.e., what types of studies must be reviewed.			
B. Authority to disapprove, modify or approve studies based upon consideration of human subject protection aspects.[2]			
C. Authority to require progress reports from the investigators and oversee the conduct of the study.[3]			
D. Authority to suspend or terminate a study.[4]			
E. Authority to place restrictions on a study.[5]			
V. THE IRB'S RELATIONSHIP TO—			
A. The top administration of the institution.			
B. The other committees and department chairpersons within the institution.			
C. The research investigators.			
D. Other institutions.			
E. Regulatory agencies.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
VI. THE MEMBERSHIP OF THE IRB.			
A. Number of members.[6]			
B. Qualification of members.[7]			
C. Diversity of members (for example, representation from the community, and minority groups), including representation by[8]—			
– Both men and women.			
– Multiple professions.			
– Non-scientific member(s).			
– Non-affiliated member(s).			
D. Alternate members (if used).			
VII. MANAGEMENT OF THE IRB.			
A. The Chairperson.			
– Selection and appointment.			
– Length of term/service.			
– Duties.			
– Removal.			
B. The IRB members.			
– Selection and appointment.			
– Length of term/service and description of staggered rotation or overlapping of terms, if used.			
– Duties.			
– Attendance requirements.			
– Removal.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
C. Training of IRB Chair and members.			
– Orientation.			
– Continuing education.			
– Reference materials (IRB library).			
D. Compensation of IRB members.			
E. Liability coverage for IRB members.			
F. Use of consultants.[9]			
G. Secretarial/administrative support staff (duties).			
H. Resources (for example, meeting area, filing space, reproduction equipment, and computer access).			
I. Conflict of interest policy.			
– No selection of IRB members by investigators.			
– Prohibition of participation in IRB deliberations and voting by investigators.[10]			
VIII. FUNCTIONS OF THE IRB.			
A. Conducting initial and continuing review.[11]			
B. Reporting, in writing, findings and actions of the IRB to the investigator and the institution.[12]			
C. Determining which studies require review more often than annually.[13]			
D. Determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.[14]			
E. Ensuring prompt reporting to the IRB of changes in research activities.[15]			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
F. Ensuring that changes in approved research are not initiated without IRB review and approval except where necessary to eliminate immediate hazards.[16]			
G. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of—			
– Unanticipated problems involving risks to subjects or others.[17]			
– Serious or continuing noncompliance with 21 CFR parts 50 and 56 or the requirements of the IRB.[18]			
– Suspension or termination of IRB approval.[19]			
H. Determining which device studies pose significant or non-significant risk.			
IX. OPERATIONS OF THE IRB.			
A. Scheduling of meetings.			
B. Pre-meeting distribution to members, for example, place and time of meeting, agenda, and study material to be reviewed.			
C. The review process.			
– Description of the process ensuring that— 1) all members review complete study documentation (see XI.B); or 2) one or more "primary reviewers"/"secondary reviewers" review the complete study documentation, report to IRB and lead discussion; if other members review summary information only, these members must have access to complete study documentation.			
– Role of any subcommittees of the IRB.			
– Emergency use notification and reporting procedures.[20]			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
– Expedited review procedure.[21] – For approval of studies that are both minimal risk and on the FDA approved list (see Appendix A). – For approval of study modifications involving no more than minimal risk.			
D. Criteria for IRB approval contain all requirements of 21 CFR 56.111.			
E. Voting requirements.[22]			
– Quorum required to transact business.			
– Diversity requirements of quorum (for example requiring at least one physician when reviewing studies of FDA regulated articles).			
– Percent needed to approve or disapprove a study.			
– Full voting rights of all members.			
– No proxy votes (written or telephone).			
– Prohibition against conflict-of-interest voting.			
F. Further review/approval of IRB actions by others within the institution (override of disapprovals is prohibited).			
G. Communication from the IRB.			
– To the investigator for additional information.[23]			
– To the investigator conveying IRB decision.[24]			
– To institution administration conveying IRB decision.[25]			
– To sponsor of research conveying IRB decision.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
H. Appeal of IRB decisions.			
– Criteria for appeal.			
– To whom appeal is addressed.			
– How appeal is resolved (override of IRB disapprovals by external body/official is prohibited).			
X. IRB RECORD REQUIREMENTS.			
A. IRB membership roster showing qualifications listed in 21 CFR 56.115(a)(5).			
B. Written procedures and guidelines.[26]			
C. Minutes of meetings.[27]			
– Members present (any consultants/guests/others shown separately).			
– Summary of discussion on debated issues.			
– Record of IRB decisions.			
– Record of voting (showing votes for, against, and abstentions).			
D. Retention of protocols reviewed and approved consent documents.[29]			
E. Communications to and from the IRB.[29]			
F. 1) Adverse reactions reports,[30] and 2) documentation that the IRB reviews such reports.			
G. Records of continuing review.[31]			
H. Record retention requirements (at least 3 years after completion for FDA studies).[32]			
I. Budget and accounting records regarding acquisition and expenditure of resources.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
J. Emergency use reports.[33]			
K. Statements of significant new findings provided to subjects.[34]			
XI. INFORMATION THE INVESTIGATOR PROVIDES TO THE IRB.			
A. Professional qualifications to do the research (including a description of necessary support services and facilities).			
B. Study protocol which includes/addresses[35]—			
– Title of the study.			
– Purpose of the study (including the expected benefits obtained by doing the study).			
– Sponsor of the study.			
– Results of previous related research.			
– Subject exclusion criteria.			
– Justification for use of any special/vulnerable subject populations (for example, the mentally impaired and children).			
– Study design (including as needed, a discussion of the appropriateness of research methods).			
– Description of procedures to be performed.			
– Provisions for managing adverse reactions.			
– The circumstances surrounding consent procedure, including setting, subject autonomy concerns, language difficulties, vulnerable populations, and other details.			
– The procedures for documentation of informed consent, including any procedures for obtaining assent from minors, using witnesses, translators, and document storage.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

DOES THE INSTITUTION HAVE WRITTEN POLICIES OR PROCEDURES THAT DESCRIBE—	YES	NO	N/A
– Compensation to subjects for their participation.			
– Any compensation for injured research subjects.			
– Provisions for protection of subject's privacy.			
– Extra costs to subjects for their participation in the study.			
– Extra costs to third party payers because of subject's participation.			
C. Investigator's Brochure (when one exists).[36]			
D. The proposed informed consent document.[37]			
– Containing all requirements of 21 CFR 50.25(a).			
– Containing requirements of 21 CFR 50.25(b), that are appropriate to the study.			
– Meeting all requirements of 21 CFR 50.20.			
– Translated consent documents, as necessary considering likely subject population(s).			
E. Requests for changes in study after initiation.[38]			
F. Reports of unexpected adverse events.[39]			
G. Progress reports.[40]			
H. Final report.			
I. Institutional forms/reports.			

Continued—

Figure 13c. U.S. Food and Drug Administration—A Self-Evaluation Checklist for Institutional Review Boards *(continued)*

A SUGGESTED SELF-EVALUATION GUIDE

CHECKLIST REFERENCES

1. § 56.101(a)
2. § 56.109(a)
3. § 56.108(a)(1) and § 56.109(e)
4. § 56.108(b)(3) and § 56.113
5. § 56.109(a) and § 56.113
6. § 56.107(a)
7. § 56.107(a–f)
8. § 56.107(a–f)
9. § 56.107(f)
10. § 56.107(e)
11. § 56.108(a)(1) and § 56.109(a and e)
12. § 56.108(a)(1) and § 56.109(d)
13. § 56.108(a)(2) and § 56.109(e)
14. § 56.108(a)(2)
15. § 56.108(a)(3)
16. § 56.108(a)(4) and § 56.115(a)(1)
17. § 56.108(b)(1) and § 56.115(a)(1)
18. § 56.108(b)(2)
19. § 56.108(b)(3) and § 56.113
20. § 56.104(c)
21. § 56.110(a–c)
22. § 56.108(c) and § 56.107(e–f)
23. § 56.109(a) and § 56.115(a)(4)
24. § 56.108(a)(1) and § 56.109(d)
25. § 56.109(d)
26. § 56.108(a–b) and § 56.115(a)(6)
27. § 56.115(a)(2)
28 § 56.115(a)(1)
29. § 56.115(a)(4)
30. § 56.108(a) and § 56.115(a)(1 and 4)
31. § 56.115(a)(3)
32. § 56.115(b)
33. § 56.115(a)(4) and § 56.104(c)
34. § 56.115(a)(7)
35. § 56.103(a) and § 56.115(a)(1)
36. § 56.111(a)(2), § 56.115(a)(1) and § 312.55
37. § 56.111(a)(4–5) and § 56.111(a)(1)
38. § 56.108(a)(4) and § 56.115(a)(3–4)
39. § 56.115(a)(3–4), § 56.115(b)(1) and § 56.113
40. § 56.115(a)(1 and 3–4)

Figure 13d. NIH, Office for Protection from Research Risks—Compliance Oversight Procedures

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December 7, 1993

TO: OPRR Staff

FROM: Director, OPRR

SUBJECT: Compliance Oversight Procedures

As you know, the Office for Protection from Research Risks (OPRR) is responsible for oversight of compliance by awardee institutions with the Department of Health and Human Services (HHS) Regulations for the Protection of Human Research Subjects (45 CFR 46) and the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals. This memorandum summarizes the procedures utilized by OPRR staff in conducting compliance oversight activities. These procedures have been developed over a period of years, and their effectiveness has been demonstrated in a number of investigations. Deviations from these procedures should occur only in extraordinary circumstances and must be approved by the Director, OPRR.

Background

As a condition of receipt of HHS support for research involving either human subjects or laboratory animals, awardee institutions must provide written Assurances of Compliance to HHS describing the means they will employ to comply with the HHS Regulations or the PHS Policy. OPRR negotiates and approves these Assurances on behalf of the Secretary, HHS. Each Assurance is a detailed document tailored to the individual institution's needs, research practices, and procedures. It must be consistent with the HHS Regulations or the PHS Policy. An Assurance approved by OPRR commits the institution and its personnel to full compliance with the Regulations or the Policy.

Continued—

Figure 13d. NIH, Office for Protection from Research Risks—Compliance Oversight Procedures *(continued)*

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In carrying out its oversight responsibility, OPRR evaluates all allegations or indications of noncompliance with either the HHS Regulations or the PHS Policy, derived from any source. All compliance oversight evaluations are predicated on the HHS Regulations or the PHS Policy and the institution's Assurance of Compliance. Therefore, OPRR holds accountable and depends upon institutional officials, committees, research investigators, and other agents of the institution to assure conformance with the institution's Assurance and thus with the Regulations or the Policy. Only through the partnership established by the Assurance can the shared responsibility to protect the rights and welfare of human subjects and the welfare of laboratory animals be effectively discharged in accordance with Sections 491 and 495 of the Public Health Service Act.

Compliance Oversight Evaluations

When OPRR initiates a compliance oversight evaluation, appropriate institutional officials are so advised, and they are informed as to 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. Except in rare circumstances when sound ethics dictates the need to act immediately, OPRR takes no action against any institution without first affording the institution an opportunity to offer information which might refute or mitigate adverse determinations. In all cases, appropriate institutional officials are afforded an opportunity to comment in writing before OPRR issues its findings.

Under HHS regulations at 45 CFR 5, documents related to compliance oversight evaluations may be subject to the provisions of the Freedom of Information Act (FOIA). In most cases, such documents are exempt from the disclosure provisions of the FOIA while the evaluation is in progress, and OPRR treats them with confidentiality. However, OPRR routinely advises appropriate HHS 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 the FOIA when OPRR issues its findings.

Under HHS regulations at 45 CFR 5b, records which can be retrieved by an individual's name or other personal identifier are subject to the provisions of the Federal Privacy Act. Information regarding OPRR's compliance oversight activities is maintained only in a system of records identifying the institution under evaluation. Records can be retrieved by institutional name or assurance number. OPRR maintains no system of records related to compliance oversight activities through which records can be retrieved by individuals' names or other personal identifiers.

Continued—

Figure 13d. NIH, Office for Protection from Research Risks—Compliance Oversight Procedures *(continued)*

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Possible Outcomes

Corrective actions based on compliance oversight evaluations are intended to remedy identified noncompliance with the HHS Regulations or the PHS Policy and to prevent reoccurrence. Because each case is different, OPRR tailors its corrective actions to foster the best interests of human research subjects or laboratory animals, the institution, the research community, and the HHS or PHS funding component. Most compliance oversight evaluations and resultant corrective actions are resolved at the OPRR level. In some instances, however, OPRR recommends actions to be taken by other HHS officials.

OPRR's compliance oversight evaluations may result in one or more of the following outcomes:

(1) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy.

(2) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy but that recommended improvements to those protections have been identified.

(3) OPRR may restrict its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by HHS until the terms of the restriction have been satisfied. Examples of such restrictions include, but are not limited to,

   (a) suspending the Assurance's applicability relative to some or all research projects until specified protections have been implemented;

   (b) requiring prior OPRR review of some or all research projects to be conducted under the Assurance;

   (c) requiring that some or all investigators conducting research under the Assurance receive appropriate human subject or animal welfare education;

   (d) requiring special reporting to OPRR.

(4) OPRR may withdraw its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by any HHS component until an appropriate Assurance is approved by OPRR.

Continued—

Figure 13d. NIH, Office for Protection from Research Risks—Compliance Oversight Procedures *(continued)*

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(5) OPRR may recommend to appropriate HHS officials or PHS agency heads

(a) that an institution or an investigator be temporarily suspended or permanently removed from participation in specific projects, and/or

(b) that peer review groups be notified of an institution's or an investigator's past noncompliance prior to review of new projects.

(6) OPRR may recommend to HHS that institutions or investigators be declared ineligible to participate in HHS-supported research (Debarment). If OPRR makes this recommendation, the Debarment process will be initiated in accordance with the procedures specified at 45 CFR 76.

Sequence of Events

The typical sequence of events to be followed in an OPRR compliance oversight evaluation is as follows:

(1) OPRR discovers or receives an allegation or indication of noncompliance with the HHS Regulations or the PHS Policy. OPRR may receive such allegations or indicators from a variety of sources, including the institution itself. Under the Regulations and the Policy, institutions are required to report any serious or continuing noncompliance to OPRR.

(2) OPRR determines that it has just jurisdiction in the matter on the basis of HHS support and/or an applicable Assurance of Compliance. (NOTE: Once jurisdiction has been established, OPRR may, at any time, require interim corrective actions under an Assurance of Compliance, or temporarily suspend the Assurance, when it considers such actions necessary to protect human research subjects or laboratory animals.)

(3) OPRR either acknowledges the institution's report of noncompliance or notifies the institution's Assurance Signatory Official of the possible noncompliance and, as necessary, requests that the institution investigate the matter and report to OPRR by a specified date. Depending upon the circumstances involved, OPRR may communicate directly with other affected institutional officials or personnel. Where the possible noncompliance involves a specific research investigator, OPRR may notify the investigator involved.

Continued—

Figure 13d. NIH, Office for Protection from Research Risks—Compliance Oversight Procedures *(continued)*

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(4) OPRR evaluates the institution's report and any other pertinent information to which it has access. If OPRR determines that the matter has not been resolved satisfactorily at this state, OPRR may request additional information from the institution or conduct an on-site evaluation of protections under the applicable Assurance of Compliance. (NOTE: On-site evaluations of protections under an Assurance of Compliance may also be conducted in the absence of specific allegations or indications of noncompliance.)

(5) Most compliance oversight evaluations can be resolved through correspondence with the institution and do not require an on-site review or a formal report of findings. In such circumstances, complainants are ordinarily informed of the outcome of OPRR's evaluation upon its completion.

(6) Where a formal report of findings is warranted, OPRR notifies the institution's Assurance Signatory Official that a formal report will be prepared. The report is forwarded to: (1) the Signatory Official with an invitation for institutional identification of errors of fact, and (ii) the complainant(s), as appropriate, with an invitation for individual identification of errors of fact.

(7) OPRR attaches any institutional or individual identification of errors of fact, and its final report is then issued to institution and complainant. If factual errors have been identified, these errors are addressed in the Preface to the final report.

(8) Except as noted above, OPRR ordinarily makes no official announcement that a final report of compliance oversight findings has been issued to institution and complainant. Once issued, however, the final report becomes available under the FOIA, as do various related documents.

Gary B. Ellis, Ph.D.

cc: Dr. Baldwin
Dr. Galasso
Mr. Lanman

E. DOE Educational Outreach Materials

OHER has developed various educational materials to increase awareness of regulations, policies, and practices concerning protection of human subjects. In addition to this handbook, the following materials are currently available:

Protecting Human Subjects Newsletter

The newsletter 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 subjects research topics.

Protecting Human Subjects Within the U.S. Department of Energy Brochure

The purpose of the brochure is to introduce researchers, research subjects, laboratory officials, and others involved in human subjects research to regulations and policies established to protect human subjects participating in research. The brochure covers topics such as informed consent requirements and IRB responsibilities. It offers a brief overview of human subjects policies and regulations.

Protecting Human Subjects Poster

This poster lists the DOE orders and Federal regulations regarding the protection of human subjects. It also refers interested persons to the DOE Human Subjects Research Program Office for further guidance.

The DOE Human Subjects Research Projects Database

The database, which is updated annually and is available to the public through Internet, contains information on all current research projects that are performed at DOE sites, performed by DOE personnel, or funded by DOE. DOE first made this information publicly available on the Internet in the spring of 1994. *(See also Chapter 12.)*

Protecting Human Subjects E-mail News Updates

The e-mail update was initiated in June 1995. The purpose of the e-mail update is to inform those involved in research at DOE of issues and concerns and to announce upcoming events and meetings. It is distributed out of OHER at DOE.

Protecting Human Subjects Internet Home Page

The purpose of the home page is to make the DOE Human Subjects Research Program more visible and to provide easy access to the educational materials listed above. Links to the Protecting Human Subjects in Research home page can be found on the URL, http://www.er.doe.gov/production/oher/humsubj/index.html.

For more information on any of these materials, contact the DOE Human Subjects Research Program Manager:

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FIFTEEN

Appendix

A. The Nuremberg Code[1]

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, 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.

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 a 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.

[1]As cited in the OPRR *1993 Protecting Human Research Subjects Institutional Review Board Guidebook*, p. A6–1. Reprinted from *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.

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 [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

B. World Medical Association—Declaration of Helsinki[2]

Adopted by the 18th World Medical Assembly
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and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
and the
41st World Medical Assembly
Hong Kong, September 1989

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly 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."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

[2]As cited in the OPRR *1993 Protecting Human Research Subjects Institutional Review Board Guidebook*, p. A6–3.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical 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 his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

C. The Belmont Report

(Document Follows)

OPRR Reports

NIH PHS HHS

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

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary

Protection of Human Subjects

Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the **Federal Register,** and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

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

Members of the Commission

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Belmont Report

Ethical Principles and Guidelines for Research Involving Human Subjects

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[1] 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.[2] 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.[3]

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

[1]Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[2]Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of pratice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[3]Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics 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 recognize 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 is 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 pres-

ents 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 conduct 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 presentation of the information to the subject's capacities. 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 arrayal 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, especially 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 shoud 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. Thus, even if individual researchers are treating their research subjects fairly, and even if 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.

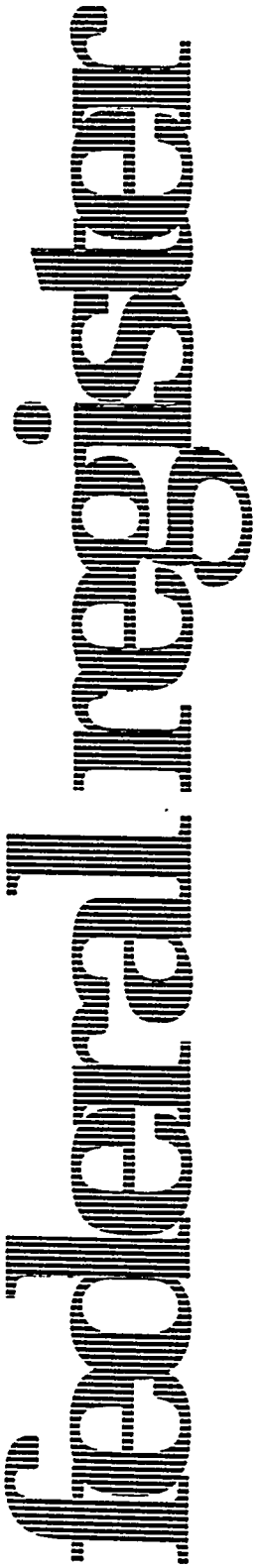
Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these 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.

[FR Doc. 79-12065 Filed 4-17-79, 8 45 am]

D. 21 CFR Part 50, et al., Protection of Human Subjects; Informed Consent; Proposed Rule (Department of Health and Human Services, Food and Drug Administration)

(Document Follows.)



Thursday
September 21, 1995

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 50, et al.
Protection of Human Subjects; Informed Consent; Proposed Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 56, 312, 314, 601, 812, and 814

[Docket No. 95N-0158]

RIN 0910-AA60

Protection of Human Subjects; Informed Consent

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; opportunity for public comment.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its current informed consent regulations to permit harmonization of Federal policies on emergency research, and to reduce confusion as to when such research can proceed without obtaining informed consent. The regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject prior to initiation of an experimental treatment. The exception would apply to a limited class of research activities involving human subjects who, because of their life-threatening medical condition and the unavailability of legally authorized persons to represent them, are in need of emergency medical intervention and cannot provide legally effective informed consent. FDA is proposing this action in response to growing concerns that current rules are making high quality acute care research activities difficult or impossible to carry out at a time when the need for such research is increasingly recognized.

DATES: Written comments by November 6, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Glen D. Drew, Office of Health Affairs (HFY-20), Food and Drug Administration, Rockville, MD 20852, 301-443-1382.

SUPPLEMENTARY INFORMATION:

I. Harmonization

Recently, the Department of Health and Human Services (HHS) authorized Institutional Review Boards (IRB's) to waive informed consent requirements for one specific National Institutes of Health-funded project under strictly defined circumstances similar to those authorized by these FDA proposed rules. (See HHS Notice of Action Related to Emergency Research Activity at 60 FR 38353 through 38354, July 26, 1995.) HHS is considering a general IRB authorization to waive informed consent requirements under the same strictly defined circumstances as those identified in the specific project waiver authorization and in the FDA proposed rule. Any HHS decision to grant a general informed consent waiver authority to IRB's for emergency research activities will be made with attention to harmonization with action on these FDA proposed rules and will be published in the **Federal Register**. It is the intent of HHS to bring the HHS (45 CFR part 46) and FDA (21 CFR part 50) regulations into harmony on this matter at the time this rule is made final.

II. Informed Consent Regulations

Much of what has become standard, accepted, medical therapies for use in acute or resuscitation clinical care has 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, in that, for example, they only work in a small percentage of those individuals who receive the therapies, so that testing of improved or additional therapies remains critically important. By permitting certain adequate and well-controlled clinical trials to occur that involve human subjects who are confronted by a life-threatening condition and who also are unable to give informed consent because of that condition, the agency expects the clinical trials to allow individuals in these situations access to potentially life-saving therapies and to result in advancement in knowledge and improvement of therapies used in emergency medical situations that currently have poor clinical outcome.

Sections 505(i), 507(d), and 520(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), and 360j(g)) require FDA to publish regulations governing the use in humans of drugs, including certain biologics and antibiotics, and devices in clinical investigations (hereafter "investigational drugs" and "investigational devices," respectively).

In 1962, amendments to the act (Section 505(d)) provided that drugs "could be approved for marketing only if they were found, on the basis of adequate and well-controlled clinical investigations, to be effective as well as safe for their intended use. Section 505(i) of the act also provided that unapproved drugs could be made available to humans for investigational use only. Section 505(i) of the act further provided for the issuance of regulations which condition the investigational use, in part, on:

> "* * * the manufacturer * * * requiring that experts using such drugs * * * certify * * * that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible, or in their professional judgment, contrary to the best interests of such human beings.

This provision created the general requirement of informed consent for investigations conducted under sections 505(i) and 507(d) of the act.

The Medical Device Amendments of 1976 revised FDA's authority to regulate medical devices and, in part, set up a statutory scheme under which devices would be classified and subjected to varying degrees of regulatory control according to classification. Section 520(g) of the act created a system under which the safety and effectiveness of new medical devices could be investigated by qualified experts. Among other requirements, section 520(g)(3)(D) of the act provided that the sponsor of clinical investigations must:

> "* * * assure that informed consent will be obtained from each human subject (or his representative) * * * except where subject to such conditions as the Secretary may prescribe, the investigator conducting or supervising the proposed clinical testing of the device determines in writing that there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative.

Section 520(g)(3)(D) of the act further provided that this determination:

> "* * * shall be concurred in by a licensed physician who is not involved in the testing of the human subject with respect to which such determination is made unless immediate use of the device is required to save the life of the human subject of such testing and there is not sufficient time to obtain such concurrence.

Sections 505(i) and 507(d) of the act permit waiver of informed consent either when "it [is] not feasible" or when it is "contrary to the best interests of such [subjects]." Section 520(g) of the act permits waiver of informed consent in life-threatening situations which "necessitates the use of such device and it is not feasible to obtain informed consent * * *."

In 1979, following the enactment of the Medical Device Amendments, FDA proposed rules revising its regulations governing informed consent (44 FR 47713, August 14, 1979). FDA issued final regulations governing informed consent in the Federal Register of January 27, 1981 (46 FR 8942). Those regulations, codified in part 50 (21 CFR part 50), apply to any clinical investigation subject to regulation by FDA under sections 505(i), 507(d), and 520(g) of the act, as well as to clinical investigations that support applications for research or marketing permits for products regulated by FDA. The agency explained its reasons for revising its regulations governing informed consent in the preamble to these final regulations. These reasons included, among others: (1) The desire to address the informed consent provision included in the device amendments; (2) the need to create a uniform set of agency-wide informed consent standards for more effective administration of the agency's bioresearch monitoring program; (3) implementation of recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; and (4) harmonization of FDA rules with those of the HHS.

Some comments on the proposed regulations questioned whether the regulations met the statutory requirements of sections 505, 507, and 520 of the act, but all comments approved of the elimination of regulatory confusion and the enhancement of human subject protections. In responding to public comments, the agency stated its belief that the standard regarding informed consent expressed in the 1962 Drug Amendments was the standard of its time, but that it was no longer the current standard of practice, given progress in the understanding of ethical principles and their relevance to biomedical research. The preamble went on to express the agency's intent to adopt a single standard that reflected both the most current congressional thinking on informed consent and the important ethical principles and social policies underlying the doctrine of consent. (See 46 FR 8942 to 8944, January 27, 1981.) In the preamble to the August 14, 1979, proposed rule, FDA further explained the requirement that a determination be made as to lack of an available alternative method of therapy that may save the life of the subject. FDA stated that this requirement:

> • • • has been added to prevent routine reliance on the exception. This additional requirement should provide guidance to investigators regarding those exceptional situations in which informed consent need not be obtained. As noted above, obtaining informed consent has come to be a standard of practice for professional clinical investigators. Defining those circumstances when informed consent need not be obtained should provide a clearer understanding of how to determine when informed consent is "not feasible."

(44 FR 47713 at 47720).

In § 50.23(a)) of the 1981 rule, FDA required informed consent except when obtaining informed consent is determined not to be feasible for the emergency use of an investigational article, where:

> • • • 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.

If immediate use of the investigational product is, in the investigator's opinion, required to preserve the life of the subject, and there is not sufficient time to obtain an independent physician's determination in advance of using the product, the use of the product is to be reviewed and evaluated in writing by a physician who is not participating in the study within 5 working days after its use (46 FR 8951, January 27, 1981).

On December 21, 1990, FDA published an interim rule in the Federal Register (55 FR 52814), amending these informed consent regulations to permit an exception from the general requirements for informed consent in certain military combat circumstances. As codified in § 50.23(d), the Commissioner of Food and Drugs (the Commissioner) is permitted to make a determination that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain battlefield or combat-related situations. The Commissioner is authorized to make such a determination when the physician(s) responsible for the medical care of the military personnel involved and the investigator(s) named in the investigational new drug application (IND) provide written justification for their conclusions that, in the use of specific investigational drugs or biologics in a specific combat-related situation, obtaining informed consent is not feasible and withholding treatment would be contrary to the best interests of the military personnel because of military combat exigencies and that the waiver of informed consent is ethically justified (52 FR 52814, December 21, 1990). This exception was upheld in the United States Court of Appeals for the D.C. Circuit in 1991. (See *Doe* v. *Sullivan*, 938 F.2d 1370 (D.C. Cir. 1991), affirming 756 F. Supp. 12 (D. D.C. 1991)).

In June 1991, the Office of Science and Technology Policy published the common Federal Policy for the Protection of Human Subjects (common rule) in the Federal Register. (56 FR 28002, June 18, 1991.) Issuance of the common rule was the result of more than a decade of work by Federal agencies and departments that conduct, support, or regulate research involving human subjects. The common rule implemented a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission). This recommendation was included in the December 1981 report of the President's Commission, entitled, "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," which stated:

> 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 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions.

(56 FR 28004, June 18, 1991)

In May 1982, the Chairman of the Federal Coordinating Council for Science, Engineering, and Technology appointed an Ad Hoc Committee for the Protection of Human Subjects. The Ad Hoc Committee agreed that uniformity was desirable among departments and agencies and worked to develop a model Federal policy, which became the common rule, 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." (56 FR 28004, June 18, 1991.) Section xx.116(d) of the common rule described the conditions under which an Institutional Review Board (IRB) was authorized to waive some or all of the elements of informed consent. This section was adopted unchanged into the HHS regulations (45 CFR part 46). (56 FR

28022, June 18, 1991.) The HHS regulations apply to research supported or conducted by HHS; they are implemented under the direction of the Office for Protection from Research Risks (OPRR) at the National Institutes of Health (NIH).

Although FDA concurred in the common rule and amended its regulations in 21 CFR parts 50 and 56 to conform them to the common rule to the extent permitted by the act, FDA regulations diverged from section xx.116(d). (56 FR 28025, June 18, 1991.) In describing the reason for this divergence, FDA stated as follows:

> The act requires that informed consent be obtained from all subjects of clinical investigations except in very limited circumstances (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)(3)(D), which establish requirements for the conduct of clinical investigations for drugs, antibiotic drugs, and medical devices, respectively). FDA does not have the authority under the act to waive this requirement.
>
> (53 FR 45679, November 10, 1988).

Thus, FDA retained its exception language dealing with individual emergency use which was contained in FDA's 1981 regulations (§ 50.23(a) through (c)); this exception remains applicable today. FDA modified other aspects of parts 50 and 56 (21 CFR part 56) in the **Federal Register** on June 18, 1991, in order to bring them into harmony with the common rule (56 FR 28025).

IRB's that are subject to both the HHS and FDA regulations have had to ensure that both the criteria in the common rule as set forth at 45 CFR part 46 and in FDA's regulation at 21 CFR part 50 are met in order to permit research to be approved.

On many occasions IRB's, functioning under HHS regulations, have been unable to approve research that required use of the waiver allowed by 45 CFR 46.116(d) because the risk involved in emergency research activities was thought to be greater than minimal and therefore the condition that the research activity "involve no more than minimal risk" could not be met. (See 45 CFR 46.116(d).)

Similarly, FDA has permitted only a very limited number of controlled trials involving investigational drugs to be conducted without informed consent under its current exception provisions. This is because § 50.23(a) permits the use of an investigational product without consent only in order to save the life of a patient, and if there is no other approved or generally recognized alternative therapy available that provides an equal or greater likelihood of saving the life of the patient. In other words, the investigator and the independent physician have had to determine that the investigational product represented the best available treatment for the patient.

The agency has permitted limited trials involving investigational drugs to be conducted by interpreting § 50.23(a) as describing the general state of circumstances that must exist as a threshold to determining that informed consent is not feasible (Refs. 1 and 2). The term "human subject," defined in § 50.3(g) as one who participates in research either as a recipient of the test article or as a control, supports the interpretation that this provision was intended to be used in the setting of an investigation conducted in accordance with principles of good clinical design, including blinding, randomization, and, where appropriate, use of a placebo as a control.

III. Background on Current Practices in the Research Community

Most therapeutic intervention in acute care and emergency research must be initiated immediately to be life-saving. 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 usually is no authorized representative of the subject available to give surrogate consent.

In 1993, the agency became aware that certain IRB's were approving research involving interventions in acutely life-threatening situations by invoking 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 participated, unknowingly, 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 (Refs. 3 through 6). As described, "deferred consent" is nothing other than post-hoc ratification. Post-hoc ratification is not genuine consent because the subject or representative has no opportunity to prevent the administration of the test article, and cannot, therefore, meaningfully be said to have consented to its use (Ref. 7).

In August 1993, IRB chairs at institutions with written assurances of compliance with HHS regulations were sent a letter by NIH's OPRR reiterating the mandate for obtaining legally effective informed consent prospectively and reminding them that the only deviation allowed by the HHS regulations is contained in 45 CFR 46.116(d), its waiver provision. The letter indicated that "deferred consent" or "ratification" fails to constitute informed consent under the HHS regulations (Ref. 8).

During the summer of 1993, the Commissioner of Food and Drugs received a number of letters from the neurology and emergency medicine communities, including the Society for Academic Emergency Medicine, the National Coalition for Research in Neurological Disorders, and the National Head Injury Foundation, expressing concern about their continued ability to conduct placebo controlled research in subjects unable to provide informed consent if FDA did not permit "implied" or "deferred consent." The Commissioner responded to these letters on September 14, 1993, indicating that FDA did not agree that "deferred" consent constituted true consent; he stated further that:

> While we recognize that it is not always possible to obtain informed consent from subjects prior to the administration of an investigational drug, we believe that it is critical to define and seek some consensus on how, precisely, patients who cannot give consent can be enrolled in such trials * * *. Before establishing new policy in this area, the Agency believes that it needs broad public and scientific input in order to determine how to balance the need for well-controlled studies with the protection of subjects' rights. Therefore, we are in the early stages of planning a workshop that will be co-sponsored by NIH to obtain necessary advice on this topic. * * * *

(Refs. 9 through 12)

Thus, although the research community is now aware that "deferred consent" does not meet the requirements of either HHS or FDA rules, and does not constitute valid informed consent, it has been given no alternative procedure, under which it may conduct emergency research under the FDA and HHS regulations, other than the limited exceptions and exemptions described previously.

IV. Patients and Research Community's Support for Change in Regulation and Congressional Interest

In correspondence, at meetings, and in published articles, the IRB and research communities have expressed their frustration at the difficulties they faced in interpreting existing regulations to fit the needs of emergency research. They have identified the need for FDA and NIH to reach a decision concerning the conduct of these studies that would result in a harmonization of the FDA and HHS regulations. Patient advocacy

groups and researchers have stressed that the research at stake is of great importance to patients and the health of the nation and care must be taken to ensure that the agencies' regulations do not inappropriately disrupt access to, or prevent the development of, potentially life-saving treatments for serious illnesses and injuries (Refs. 13 through 20). The IRB and research communities have stressed that a common position adopted by both FDA and NIH will help eliminate confusion concerning which regulations, FDA or HHS or both, need to be followed and will eliminate conflicting requirements that must be met in order for the research to proceed. This is especially true in cases where a majority of the study sites are subject to both sets of regulations. Finally, they have argued that it is appropriate that FDA and NIH agree on the basic conditions and the ethical conduct of acute care research in order to carry out PHS's dual leadership responsibility to promote sound biomedical research while helping to protect the rights and welfare of human subjects (Refs. 21 through 25).

The research addressed by this proposed regulation is believed to constitute a small fraction of all clinical research. This is because, in some instances, an individual may be unconscious or incompetent to give informed consent, but immediate involvement in research is not needed to promote healing or to prevent death. In those instances, it may be possible to delay participation in research until consent from a legally authorized representative can be obtained. There are also medical conditions that predictably occur in given identifiable patient populations. In such cases, prior informed consent can be obtained from potential future subjects before the intervention occurs because the patient will understand the likelihood of the future need to participate in research when consent cannot be obtained. In other cases, such as events that occur regularly in already hospitalized, acutely ill patients, the majority of subjects will have a legally authorized representative readily available to provide surrogate consent. In these instances, the research may, in accord with the provisions of the law of the jurisdiction, proceed without invoking a waiver of informed consent. In those cases that remain, research can only be conducted in the absence of informed consent.

A May 23, 1994, hearing of the Subcommittee on Regulation, Business Opportunities, and Technology, House Committee on Small Business, then chaired by Representative Ron Wyden, addressed problems encountered in securing informed consent of subjects in clinical trials of investigational drugs and medical devices (Ref. 26). In Representative Wyden's opening remarks, he acknowledged that while informed consent is an essential component of biomedical research, there are certain conditions under which obtaining informed consent in the classic sense may not be possible, and it is imperative that testing of potentially life-saving therapies go forward. He further asserted that contradictory and confusing Federal policies on informed consent have fostered inconsistent application of the Federal requirements on the part of investigators and IRB members. Representative Larry Combest, in his opening statement, expressed his desire for HHS Secretary Donna Shalala to establish consistent Federal rules related to obtaining informed consent during research on unapproved drugs and medical devices. He emphasized the need to harmonize HHS and FDA regulations while streamlining the approval process.

Researchers, IRB members, device and drug manufacturers, and ethicists testified about the state of emergency research and the negative impact current regulations have had on the ability of such research to proceed; the ethical issues surrounding the conduct of emergency research in situations where human subjects are not competent to give informed consent; and the need for better guidance from Federal agencies. Representatives from NIH and FDA testifying at the hearing acknowledged the need to further examine the issue of circumstances under which research activities may go forward when informed consent cannot be obtained.

On October 25, 1994, persons associated with several professional organizations, institutions, patient advocacy groups, and the bioethics community met at the Coalition Conference of Acute Resuscitation and Critical Care Researchers (the Coalition) to discuss the current Federal regulations regarding informed consent for participation in research. Observers from the legal community, congressional and senate offices, FDA, and the NIH's OPRR also attended.

The Coalition conference was convened under the joint sponsorship of the American Heart Association and the Society for Academic Emergency Medicine and included representatives from the American Academy of Clinical Toxicology, the American Association for the Surgery of Trauma, the American College of Cardiology, the American College of Emergency Physicians, the Applied Research Ethics National Association, the Emergency Nurses Association, the Joint Section on Neurotrauma and Critical Care, the National Head Injury Foundation, and the Society of Critical Care Medicine.

Following this Coalition conference, the Coalition developed a consensus document to offer recommendations to help resolve some of the issues concerning informed consent and waiver of consent in emergency research. The American Heart Association and the Society for Academic Emergency Medicine submitted the consensus statement to FDA. The consensus document has been endorsed by a number of professional organizations, including the American Academy of Clinical Toxicology, the American Academy of Pediatrics' Pediatric Emergency Medicine Collaborative Research Committee and Section on Emergency Medicine, the American Association for the Surgery of Trauma, the American Autoimmune Related Diseases Association, the American Brain Injury Consortium, the American College of Emergency Physicians, the Applied Research Ethics National Association, the Emergency Nurses Association, the Medical Device Manufacturers Association, the National Head Injury Foundation, the New England Biomedical Research Coalition, the Society for Pediatric Emergency Medicine, the Society for Critical Care Medicine, and the National Association of EMS Physicians.

The consensus document described the importance of emergency research, provided background on the current regulations that govern waiver of consent in clinical research trials, and reviewed current issues arising from the use of waiver of consent in emergency research. The consensus document concluded that there are circumstances under which it is not feasible to obtain consent for enrollment into a protocol involving emergency research; and that, in these circumstances, patients are vulnerable both to risks associated with research, but also to being denied benefits offered by research interventions when no effective standard treatment is known. The consensus document contained recommendations "which should be met when the critical nature of the illness or injury, or the need for rapid treatment intervention, precludes prospective consent for participation in emergency research" (Ref. 22).

On January 9 and 10, 1995, FDA and NIH cosponsored a Public Forum on Informed Consent in Clinical Research Conducted in Emergency

Circumstances. as was proposed by the Commissioner of Food and Drugs in his letters of September 14. 1993 (Refs. 9 through 12 and Refs. 23 and 24). The Coalition consensus document was presented and discussed as well as other models for changing the regulatory paradigm (Ref. 25). Participants at that public forum affirmed the need to protect research subjects while allowing clinical research to proceed if the research subjects are in a life-threatening situation. available treatments are unproven or unsatisfactory. and immediate intervention is necessary if the intervention is to be of benefit (Refs. 25 and 26). Many participants expressed concern that the current regulations value individual autonomy and the right to informed consent at the expense of the principles of beneficence and justice. They argued that when the expected outcome of standard therapy is poor. and a promising research intervention is available. the principle of beneficence should be permitted to take precedence over the principle of autonomy (Ref. 23). A minority view expressed was that one cannot ethically assume that acutely ill. incompetent patients would. if they were able. choose to participate in a research protocol. Those supporting this view believed that to exclude these patients from a research protocol did not discriminate against them. but rather respected their autonomy (Refs. 24. 27. and 28).

Forum participants discussed the ethical. regulatory. and operational challenges faced by IRB's and by emergency and acute care researchers. as well as ideas for resolving those dilemmas in an ethical way. Speakers emphasized that the "golden hour" or the "window of opportunity" following acute injury is a concept on which modern trauma care is based. "Nearly all patients who die from injury in the first 24 hours do so from processes set in motion at the time of injury. Any therapeutic intervention must [therefore] be begun immediately to interrupt the injury-induced cascade of body reactions leading to death. That is. intervention must be instituted in the field by the first response team of paramedics. in the trauma room in the operating room. and in the surgical critical care unit" (Ref. 23. p. 277).

Participants agreed that current resuscitation modalities are only minimally effective in saving lives and improving outcome and quality of life. Trauma and acute care physicians reported frustration in employing time-honored treatments that provide little benefit to their patients. Many expressed concern that. because of the current Federal regulations. emergency care professionals are hesitant to conduct appropriately designed clinical trials which are needed to validate or discredit current or innovative treatments. During the Public Forum. participants provided numerous examples of the chilling effect that the current regulations have had on the conduct of clinical research. including cardiopulmonary resuscitation (CPR) studies. and studies of acute trauma. overdose. acute asthma exacerbations. cardiac arrest. head injury. seizures. and stroke (Refs. 23. 24. and 25).

Representative of the studies discussed was one in the area of sudden cardiac arrest. Each year. approximately 350.000 people in the United States suffer a sudden cardiac arrest. Most die. while many others are irreversibly harmed by complications such as brain damage. In the cases of patients who survive. the risk of recurrence is high and the protection offered by easily implantable cardioverter-defibrillators exemplifies the important successes that can be achieved. One of the most critical challenges is to find ways to improve the initial survival rate of individuals who are typically unresponsive and unable to communicate. Currently. despite efforts to instill basic life support education (i.e.. standard CPR techniques). only a small percentage of individuals who suffer sudden out-of-hospital cardiac arrests are resuscitated by bystanders. Few survive to leave the hospital. This percentage may be as low as 1 to 3 percent in some large metropolitan areas. with the best results estimated to be only in the 25 percent range. Given the large number of sudden cardiac arrests annually in the United States alone. even small improvements in care offer enormous life-saving potential (Ref. 29).

Standard CPR methodology was largely developed on a mechanistic and theoretical basis. Improvement or rigorous challenge of the methodology is complicated by the difficulty in obtaining approval to undertake studies in out-of-hospital cardiac arrest victims. The inability of most cardiac arrest victims to provide the requisite informed consent has proved a significant barrier to evaluating either treatment options available in other countries. or new techniques devised in the United States (Ref. 29).

Participants asserted that. without validation of standard treatment. many patients are now essentially participants in uncontrolled "experiments" when they receive emergency care. These "experiments." however. do not yield data on which progress in rational medical decisionmaking can be based. For example. one IRB would not approve a protocol for a randomized clinical trial of high dose versus standard dose epinephrine in cardiac arrest. even though some clinicians at that institution used high dose epinephrine in some cases and others did not. The ultimate result was that patients were not allocated randomly to high or standard dose (Ref. 30). The scientific question of which dose was better could be realistically addressed only in a controlled trial with subjects randomly allocated to each dosage level in order to assure that multiple variables caused by differences in physicians or other features of resuscitation technique did not confound the data.

The majority of participants in the Public Forum recommended that NIH and FDA change their regulations so that they are clear and consistent and that NIH 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. Participants recommended that a short- and long-term solution be sought which would permit this research to proceed. The short-term solution would be needed if a change in the regulations could not be accomplished quickly.

Since the time of the Public Forum. the Assistant Secretary for Health. the NIH Director. and the Commissioner of FDA have received a number of letters urging NIH and FDA to clarify their regulations to allow for waiver of informed consent in appropriate emergency research circumstances. On March 31. 1995. the Coalition of Acute Resuscitation and Critical Care Researchers submitted a statement containing over 1.300 signatures requesting that NIH and FDA: (1) Recognize the need for clinical research in emergent circumstances where informed consent may not be feasible; and (2) issue an interpretation of the existing Federal regulations to allow the performance of this research.

V. Statutory Basis for These Regulations

Sections 505(i). 507(d). and 520(g) of the act direct the Secretary (and. in accordance with section 903 of the act (21 U.S.C. 394). FDA) to issue regulations establishing conditions under which investigational use of drugs and devices by qualified experts will be permitted. For drugs (including biological drugs and antibiotics) and devices. the statute specifies that the agency must include among these conditions that the product manufacturer or sponsor require the

expert studying the product to obtain informed consent from the subjects or their representatives.

The only exceptions from the informed consent requirement for drugs are where the investigators "deem it not feasible or, in their professional judgment, contrary to the best interests" of the subjects (sections 505(i) and 507(d) of the act). The language of these provisions makes it clear that Congress contemplated that informed consent could be waived in the context of placebo-controlled drug trials: "[the investigators] will inform any human beings to whom such drugs, *or any controls used in connection therewith*, are being administered * * * and will obtain the consent of such human beings or their representatives, except where [not feasible or contrary to their best interests]" (emphasis added). The 1962 Drug amendments, which included section 505(i) of the act, added the requirement that drugs be shown to be not only safe, but also effective through "adequate and well-controlled investigations, including clinical investigations," by experts qualified to evaluate effectiveness (section 505(d) and (e)). Section 505(i) of the act, then, authorized FDA to establish the conditions for the conduct of these required studies in humans. (See also section 507(d) of the act.)

The 1962 amendments were adopted following the thalidomide tragedy, in which women were given the drug without being informed that the drug was experimental, or that they were research subjects, or that the safety of the drug had not been established. (See generally legislative history discussion at 44 FR 47714–47715, August 14, 1979.) Although the House bill would have required informed consent in all clinical trials of drugs, the version reported out of Conference allowed the exceptions that became law (H.R. Rept. No. 2526, 87th Cong., 2d sess., October 3, 1962, pp. 4 and 5). Professional responsibility, based on "the greatest exercise of conscience," was accepted in permitting administration of investigational drugs without informed consent (108 Congressional Record 22038, 22042–43, 87th Cong., 2d sess., October 3, 1962).

The only exceptions from the informed consent requirements for devices are where the investigator determines "there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device and it is not feasible to obtain informed consent from the subject and there is not sufficient time to obtain such consent from his representative" (section 520(g)(3)(D) of the act). In addition, "unless immediate use of the device is required to save the life of the human subject," and there is insufficient time to obtain the concurrence of a licensed physician not involved in the testing, such a physician must concur in the determination (section 520(g)(3)(D) of the act). The exceptions to require informed consent are "subject to such conditions as the Secretary may prescribe."

The context of this provision also is a statutory amendment allowing exemptions to permit investigational use to study the products' safety and effectiveness (section 520(g)(2)(A) of the act). The Medical Device Amendments of 1976, which included section 520(g), added a system of classifications and premarket approval for certain devices (section 513 of the act (21 U.S.C. 360c)). The amendments contemplated that, with certain exceptions, effectiveness would be determined based on "well-controlled investigations, including clinical investigations where appropriate," by experts qualified to evaluate effectiveness (section 513(a)(3) of the act).

Congress was explicit about the purpose of section 520(g) of the act: "to encourage to the extent consistent with the protection of the public health and safety and with ethical standards, the discovery and development of useful devices intended for human use and to that end to maintain optimum freedom for scientific investigators in their pursuit of that purpose" (section 520(g)(1)). The conditions required by section 520(g), then, are to be interpreted within the context of this stated general purpose of providing freedom to the investigators within ethical standards and health and safety protections.

Both the House report on the bill containing the language that became law in section 520(g) of the act and the Conference report refer to the study by the National Commission on the Protection of Human Subjects concerning informed consent. (See H.R. Rept. No. 853, 94th Cong., 2d sess. 44 (1976); H.R. Rept. No. 1090, 94th Cong., 2d sess. 64 (1976).) This Commission, established by the National Research Act in 1974, was to study the basic ethical principles underlying the conduct of biomedical and behavioral research involving human subjects. Congress clearly intended HHS to act in response to the Commission's efforts (id.). The Commission issued numerous reports, including a report on Institutional Review Boards. (See generally 44 FR 47716, August 14, 1979 for a listing of the reports.) This IRB report stated that "investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share this responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of human subjects of their research" (43 FR 56174, November 30, 1978).

The Commission's articulation of the basic ethical principles that should underlie the conduct of biomedical research involving human subjects is the Belmont Report, which was prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1978 (44 FR 23192, April 18, 1979). In proposing its informed consent regulations in 1979, FDA noted the congressional purpose reflected in both the Drug Amendments of 1962 and the Medical Device Amendments of 1976, to require that biomedical research be conducted "in accordance with the highest contemporary ethical standards" (44 FR 47718, August 14, 1979). In interpreting sections 505(i), 507(d), and 520(g) of the act in 1995, it remains consistent with congressional intent to apply the principles of the Belmont Report in their applications by ethicists to current research issues. As discussed in detail in the following section, this proposed rule to provide an exception from the requirement of informed consent is supported by contemporary application of the ethical principles of the Belmont Report.

Congress did not specifically address the fact that the statutory language containing the informed consent exemption requirements for investigational devices differed from those for investigational drugs enacted 14 years earlier. However, as the agency discussed in proposing its informed consent regulations in 1979, the actual policy followed by FDA regarding the drug informed consent exception was very similar to the policy being proposed for devices (44 FR 47718). In originally promulgating its regulations in part 50 on the protection of human subjects, FDA chose to apply the same standards to drug and device research. In order to preclude confusion that might result from different systems for informed consent for drug and device research and to implement congressional purpose reflected in both the Drug Amendments of 1962 and the Medical Device Amendments of 1976 (i.e., to require conduct of research in accordance with contemporary ethical

standards), FDA is again proposing to apply the same standards to drug and device research.

Sections 505(i), 507(d), and 520(g) of the act authorize the agency to establish the conditions for investigational use. In the proposed rule, FDA would establish conditions that satisfy the statutory criteria for exceptions from the informed consent requirement and allow for safe use under ethical standards for research.

Under sections 505(i) and 507(d) of the act, a showing that obtaining informed consent is not "feasible" is alone sufficient to permit an exception to the requirement. Research without informed consent is also authorized in drug studies based upon professional judgment regarding the "best interest" of the subjects. Under section 520(g), informed consent is required unless there is a written determination that (1) "There exists a life threatening situation involving the human subject of such testing which necessitates the use of such device," (2) "it is not feasible to obtain informed consent from the subject," and (3) "there is not sufficient time to obtain such consent from his representative." In addition, a licensed physician who is not involved in the testing must agree with this three-part determination unless there is not sufficient time to obtain such concurrence. Consequently, circumstances that satisfy the statutory informed consent exception criteria for investigational devices will also satisfy the criteria for investigational drugs.

The exception from the informed consent requirement permitted by the proposed rule would be conditioned upon various findings by an IRB. First, the subjects must be in a situation that is: (1) Life-threatening, (2) where available treatments are unproven or unsatisfactory, and (3) the collection of valid scientific evidence is necessary to determine the most beneficial intervention (§ 50.24(a)(1)). In addition, the opportunity to be in the study must be in the interest of the subject because the life-threatening situation necessitates intervention and the risk of the study is reasonable in light of the medical condition and what is known about the risks and benefits of current therapy and of the investigational intervention (§ 50.24(a)(3)). With regard to the study itself, it must be research that could not practicably be carried out without the informed consent waiver (§ 50.24(a)(4)).

These conditions satisfy the criterion included in sections 505(i) and 507(d) of the act regarding the best interest of the subject. They also satisfy the criteria in section 520(g) of the act that the subject be in a "life threatening situation" which "necessitates the use of such device." The proposed rule would limit the exception to the narrow circumstance in which both (1) intervention is needed because of the subject's medical condition, and (2) the collection of valid data is needed because of the absence of proven satisfactory available treatment for the condition. The proposed rule thus gives double weight to the statutory "necessitates" criterion.

The agency's proposed implementation of the "necessitates" criterion also would permit administration of either the test product or a control product, in keeping with the legislative intent to permit scientific investigation to demonstrate safety and effectiveness. Randomized placebo-controlled or active-controlled studies may be needed to demonstrate the effectiveness of products for life-threatening, as well as nonlife-threatening, conditions. As discussed in more detail below, this interpretation is also consistent with the ethical principles in the Belmont Report. For example, the principle of beneficence supports research that ultimately "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" (Belmont Report, 44 FR 23192 at 23194, April 18, 1979).

In issuing current § 50.23(a), permitting exceptions from obtaining informed consent, the agency included an additional criterion not required by section 520(g)(3)(D) of the act (44 FR 47720, August 14, 1979). This provision of the regulation, codified at § 50.23(a)(4), was added "to prevent routine reliance on the exception" (44 FR 47720, August 14, 1979). In final form, this subsection required that "[t]here 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." The proposed new § 50.24(a) would permit use of the test product when there is an alternative unproven or unsatisfactory therapy in general use that may be equally likely to save the subject's life. Section 50.24(a)(3) would allow for "reasonable" risk, given what is known about the risks and benefits of the test product, the alternative therapy, and the medical condition. The narrowly circumscribed situation described in § 50.24, as well as additional safeguards, such as public disclosure prior to beginning the study, protects against "routine reliance" on this exception to conduct research without informed consent.

Section 50.24 also would require, in accordance with the criterion in sections 505(i), 507(d), and 520(g) of the act, that obtaining informed consent not be "feasible." This regulation would restrict determinations of infeasibility to those situations in which: (1) The subjects are unable to give consent because of their medical condition, (2) the product must be administered before it is feasible to obtain consent from legally authorized representatives, and (3) individuals likely to be eligible cannot reasonably be identified prospectively (§ 50.24(a)(2)). Thus, section 50.24(a)(2) also incorporates the required criterion of section 520(g) that there be insufficient time to obtain consent from a representative.

Section 50.24 would require approval of the protocol by an IRB, which is also required to have at least one member who is a licensed physician not otherwise involved in the research protocol (or such a consultant) who concurs with the protocol. That physician's concurrence is in keeping with the provision of 520(g)(3)(D) for concurrence by such an individual that the criteria for testing without informed consent have been satisfied. In most, if not all, instances under § 50.24 there will be a need for "immediate use" to save the subject's life and not sufficient time following the onset of the life-threatening condition to obtain the concurrence by an independent physician and, therefore, there will be no statutory requirement for such concurrence. Nevertheless, the agency believes that concurrence with the protocol by an independent physician associated with the IRB is another valuable protection for the subject and additional assurance that the statutory intent of independent physician concurrence will be satisfied.

For the reasons discussed above, the provisions of § 50.24 satisfy all of the statutory criteria of sections 505(i), 507(d), and 520(g) of the act for permitting exceptions to the informed consent requirements for investigational drug and device uses.

Section 50.24 also contains additional protections for the health and safety of the research subjects (e.g., establishment of an independent data and safety monitoring board), as authorized by, and in keeping with the purposes of sections 505(i), 507(d), and 520(g) of the act. This proposed regulation is also authorized by section 701(a) of the act, which provides general authority to issue regulations for the efficient enforcement of the act.

The conforming amendments to regulations governing drug and device investigations and marketing are authorized by sections 502, 503, 505, 506, 510, 513, 514, 515, 516, 518, 519, 520, 701, and 801 of the act and section 351 of the Public Health Service Act (21 U.S.C. 352, 353, 355, 356, 360, 360c, 360d, 360e, 360f, 360h, 360i, 360j, 371, and 381, and 42 U.S.C. 262)

VI. Ethical Basis for These Regulations

In developing this proposed regulation, FDA has carefully considered the basic ethical principles that underlie research to ensure that it is consistent with those principles. The agency is convinced that the research described in this section is ethically permissible.

The current FDA and HHS IRB and informed consent regulations are based, in large part, on the ethical principles discussed in the Belmont Report. As discussed in that report, the three basic ethical principles that are relevant to research involving human subjects are the principles of respect for persons, beneficence, and justice.

The principle of respect for persons incorporates two general rules of ethical behavior: (1) Competent individuals must be treated as autonomous agents, that is to say, persons who are legally and morally competent to understand the risks and benefits of a proposed research activity must provide prior, uncoerced informed consent before they may be enrolled as research subjects; and (2) persons whose autonomy is absent or diminished may participate in research only if additional protections are provided for them. The proposed rule recognizes that subjects who are candidates for emergency research will not meet the condition of being fully competent. In many cases, they will be totally incompetent. Such potential subjects, if they are to be enrolled in research, must be provided with special additional protections. The special protections proposed in this rule for subjects of emergency research include prior FDA and community consultation on the research, public disclosure, and careful mandatory oversight of the welfare of subjects by a data and safety monitoring board. These special protections are described below.

The principle of beneficence requires that the risks associated with a research activity are reasonable in the light of expected benefits and it also requires that the chance for benefits from participation be maximized, and the risk of possible harms be minimized, consistent with sound research design.

The principle of justice requires that the burdens and benefits of participation in research be equitably distributed across the entire population in the place or region where the research is conducted. That means, in general, that racial, ethnic, gender, and economic status should not be used as exclusion criteria for participation in research. It further means that persons who are eligible for participation in the research because of their disease or condition, should be provided reasonable opportunity to participate in research until the research cohort is fully recruited. Experience has repeatedly shown that requiring surrogate consent from legally authorized representatives tends to inhibit equitable inclusion in the study because surrogate consent is more easily obtained from family members of Caucasians than from family members of minorities, and it is more easily obtained from family members of middle and upper income persons than from persons of lower income (Ref. 31). Waiving the requirement for informed consent from potential subjects and their surrogates helps to provide for an equitable distribution of both burdens and benefits of emergency research in a manner that meets the requirements of justice.

The Belmont Report notes that "[t]hese 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." (44 FR 23193, April 18, 1979.) The Belmont Report did not, therefore, address resolution of conflicts among these ethical principles that might be occasioned by a particular research protocol, but it did provide a framework within which conflicts among the principles could be resolved.

The National Commission did not explicitly address the issue of research involving the comatose patient. However, in March 1983, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued its "Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subject." In its report, the President's Commission identified research on the comatose as an issue worthy of further consideration. In its discussion, it noted that

> It is settled law that physicians and hospitals may assume that an emergency patient would consent to life-saving treatment; such treatment may therefore be initiated without express consent. The legal principle is based, however, on the provision of standard care. It is not so clear, however, whether one should assume that an emergency patient would consent to participation in research on new or experimental treatment. (Ref. 32)

The agency has considered the ethical principles set forth in the Belmont Report in the formulation of this rule. It has also engaged in extended public dialogue to resolve the difficulty noted by the President's Commission. The exception from informed consent for investigations involving life-threatening conditions would apply only to subjects not in a position to exercise autonomy. These subjects will be in a life-threatening situation which necessitates emergency intervention. Thus, in accord with the principle of respect for persons, persons in these situations are entitled to special protection.

In emergent situations, protection is provided and the principle of respect for persons is satisfied if, in circumstances of clinical equipoise, either the test therapy or its historic alternative is provided, even without specific consent. When the relative benefits and risks of the proposed intervention, as compared to standard therapy, are unknown, or thought to be equivalent or better, there is clinical equipoise between the historic intervention and the proposed test intervention. Clinical equipoise would exist, according to testimony presented at the January 1995 FDA/NIH Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances, whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than, the standard treatment (Ref. 23).

This proposed rule is also consistent with the principle of beneficence. The principle of beneficence maximizes possible benefits and minimizes possible harms. In order to avoid harm, one must know what is harmful. In emergency medicine, the standard of care may not have been validated—it may be beneficial or it may be harmful. The principle of beneficence dictates that knowledge be gathered when there is clinical equipoise between established and proposed interventions, through the conduct of research. Beneficence can be assured by the collection of valid scientific evidence, including evidence derived from randomized controlled clinical trials, in order to determine whether the particular intervention is beneficial. Harms are minimized, in part, by careful monitoring of the study by an independent data and safety monitoring board that regularly compares study

data with preestablished "stopping rules" designed to terminate the study before any serious harm occurs.

The principle of justice is also pertinent to this proposed rule. Systematically excluding persons who are unable to give informed consent and who have no surrogate to consent for them from research may be discriminatory, as noted above. An inability to consent, or lack of an authorized representative, should not in itself be a reason for excluding persons from participating in potentially beneficial and scientifically well-designed, controlled, studies (Refs. 33 and 34).

VII. Description of the Proposed Rule

A. Introduction

Section 50.24 will be applicable only to that limited subset of research activities that involve individuals who are in a life-threatening situation and for whom available treatments are unproven or unsatisfactory (e.g., have poor clinical outcome or leave individuals with substantial mortality or major morbidity). FDA believes that evidence submitted at the Public Forum on the chilling effect of current regulations on the care and medical management of such persons in life-threatening situations, including impairing their access to potentially life-saving therapy, justifies the prompt issuance of regulations governing research on such subjects. Thus, FDA intends to issue a final rule, responding to comments received on this proposed rule, promptly following the 45-day comment period.

B. Scope

Section 50.24(d) will require that all protocols that involve a product regulated by FDA and that involve the possibility of invoking an exception under this section are to be performed under a separate IND or a separate Investigational Device Exemption (IDE).

For medical devices, this means that a sponsor may not submit the investigation to an IRB as a nonsignificant risk device (21 CFR 812.2(b)). All device investigations are to be submitted to the agency as separate IDE's, prominently identified as IDE's that propose to invoke the exception in this rule. If the sponsor has already submitted an IDE to the agency for the medical device, the sponsor may cross-reference information in that IDE. The purpose of proposing to require a separate IDE is to ensure that there are 30 days before commencement of the trial in order to permit agency review of the protocol and supporting information.

For drugs, this means that the exemptions from the requirement to submit an IND, contained in 21 CFR 312.2(b), may not be invoked for investigations of a drug product that is lawfully marketed in the United States if the investigation involves potential invoking of § 50.24. The agency believes that investigations that propose to involve individuals who are unable to give informed consent do not meet the requirements of § 312.2(b)(iii), i.e., the use in this subject population would increase the risks or decrease the acceptability of the risks associated with the use of the drug product and, therefore, agency review of the IND is appropriate. All drug investigations will be submitted to the agency as separate IND's, prominently identified as IND's that propose to invoke the exception in this rule. If the sponsor has already submitted an IND to the agency for the drug product, the sponsor may cross-reference information in that IND. The purpose of proposing to require a separate IND is to ensure that there are 30 days before commencement of the trial in order to permit the agency to review the protocol and supporting information.

C. IRB Responsibilities

Section 50.24(a) gives the IRB the primary responsibility for determining that the research meets the requirements of this proposed rule. In the Coalition's consensus statement, the Coalition recommended that the interests, rights, and welfare of subjects in emergency research trials be protected by special safeguards applied by IRB's. It recommended further that because IRB's have good insight into local practice, subject populations, and the capabilities of researchers, institutions and resources, that IRB's should be the primary unit responsible for maintaining oversight of these clinical trials. The majority of participants at FDA/NIH Public Forum also expressed support for this responsibility being placed on IRB's.

At the congressional hearing and at the Public Forum, some individuals expressed concern about placing this responsibility with IRB's that charge for their services and that are not physically located where the research is to be conducted, so called, "independent IRB's." The agency has considered these concerns, but believes that duly constituted IRB's that fulfill the requirements of part 56 (21 CFR part 56) and § 50.24, including paragraph (a)(5) which will require consultation with the communities from which the subjects will be drawn and public disclosure, will ensure that the rights and welfare of research subjects are protected. The agency has permitted independent IRB's to review research since 1981. The agency has acknowledged that independent IRB's that lack members from the area of the research site may have difficulty acquiring knowledge of community attitudes, information on conditions surrounding the conduct of the research, and the continuing status of the research. FDA has advised these IRB's, at conferences and in written educational materials, to be particularly sensitive to meeting all requirements of the regulations.

This regulation would permit the IRB to approve research without requiring that informed consent be obtained if the IRB determines and documents that it is approving such research for the reasons given in § 50.24(a).

D. IRB Documentation

This regulation will require the IRB to document that it considered each element in § 50.24(a) and found that each element was met by the proposed research. The agency believes that this documentation is necessary to ensure that the IRB is adequately protecting the rights and welfare of human subjects.

Under § 50.24(e), an IRB would be required to document its findings when it cannot approve the research either because the research does not meet the criteria in § 50.24 or because of other relevant ethical concerns. The IRB is to provide this information in writing to the research sponsor. The sponsor of the research must share this information with FDA, and investigators, and other IRB's that are asked to review this or a substantially equivalent trial. FDA believes that sharing IRB information with these entities concerned with the study will enhance the protection provided to research subjects by establishing communication among IRB's on this important issue. IRB concerns about the approvability of studies may identify to the sponsor and FDA issues that need to be addressed in the research such as the need to alter the study design to better protect the rights and welfare of research subjects. The sponsor's sharing of these concerns with other investigators and IRB's that are asked to review this or substantially equivalent research, assures that all relevant IRB's and investigators will be aware of concerns noted by other IRB's and will have the opportunity to assess those concerns in their review of the research activity.

Because IRB's that review FDA-regulated research may be institutionally-based, independent of an

institution, commercial, established by the sponsor of the research, or established by a group of investigators, it is possible for an investigator to seek approval of an investigation from more than one IRB. Thus, if the study is disapproved by one IRB, it is possible for the investigator to seek approval from another. The agency believes that the provision requiring the sharing of information will enable any IRB that is asked to review the study to take into account relevant ethical concerns raised by another IRB.

This requirement would not add an additional documentary burden to IRB's because under § 56.115(a)(2), the IRB is required to document the basis for disapproving any proposed research and to prepare a written summary of the discussion of controverted issues and their resolution. The proposed requirement in § 50.24(c), for IRB retention of records and for their availability during an inspection, is identical to that required for records maintained pursuant to part 56.

E. Criteria for IRB Approval

Section 50.24(a)(1) would require that the IRB determine that:

> * * * 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 trials, is necessary to determine what particular intervention is most beneficial.

The agency believes that an IRB can determine that the subjects are in a life-threatening situation if it determines that the medical condition being treated by the proposed intervention poses an imminent risk of loss of life. FDA considers treatments to be unproven when, for example, their safety and effectiveness have not been established in adequate and well-controlled clinical trials. FDA believes that unsatisfactory treatments include those treatments which fail to prevent a significant proportion of deaths or permanent disabilities in the population of interest. As discussed earlier, in order to learn what is harmful or beneficial, the intervention or activity must be subjected to adequate and well-controlled trials, including, where appropriate, trials involving a placebo. Determining the risks and benefits of intervention for potentially life-saving therapies will enable physicians to better evaluate the appropriate treatment for individual patients.

As the Coalition noted in its consensus statement:

> Patients deserve and expect modern, safe, and effective medical care when they are acutely ill or injured. We believe the public desires advances in acute emergency and critical care and understands that research is required to improve medical care. The benefits of emergency research include potential improvement in survival and the quality of life following many life threatening conditions that otherwise would have dismal outcomes. The risk of not doing emergency research is denying promising new treatments to individual patients with conditions that currently have no effective therapy, or to future patients with the same devastating condition. (Ref. 22.)

Section 50.24(a)(2) defines when obtaining informed consent is not feasible. The agency believes that the first criterion (§ 50.24(a)(2)(i)) generally will be met if, once the medical condition develops, the potential subjects would not be able to give informed consent as a result of the medical condition. Examples of situations in which obtaining informed consent from the subject may not be feasible include individuals who have suffered a cardiac arrest, severe head injury, or other catastrophic medical or traumatic event.

Section 50.24(a)(2)(ii) would require the IRB to determine that it is necessary to administer the intervention before it is feasible to obtain informed consent from a legally authorized representative. It would require the IRB to consider the consequences of waiting to administer the intervention until a legally authorized representative can consent on behalf of the subject. This criterion recognizes the Coalition's concern that "the test therapy for these catastrophic conditions must be given immediately after the acute injury or illness to have any possibility of benefit." If the window of time is narrow, it will be difficult or impossible to identify a legally authorized representative especially for patients whose identities are unknown at the time of presentation.

Section 50.24(a)(2)(iii) would require the IRB to determine that there is no reasonable way to identify prospectively the individuals likely to become eligible for the research because the emergence of the condition to be studied cannot be predicted reliably in particular individuals. The agency believes that when there is a reasonable way to prospectively identify such individuals, that efforts should be made to obtain prospective consent for the particular protocol from those subjects.

Section 50.24(a)(3) describes why the research intervention is in the best interests of subjects. As discussed earlier, the agency expects clinical equipoise to exist in protocols that would be approved under this section. Clinical equipoise exists when the relative benefits and risks of the proposed intervention are unknown, or thought to be equivalent or better than standard therapy. Clinical equipoise has been described as existing when at least a reasonable minority of medical professionals believe the test article is as good as or better than the standard treatment or that the standard treatment to be tested is no better than placebo. The agency expects that evidence from animal studies, previous use in humans (for other indications), similarity to other products used in humans, and other evidence, could be used to document clinical equipoise.

Section 50.24(a)(4) would require the IRB to determine that the study could not practicably be conducted without the waiver. This regulation will not permit waiver of informed consent in instances in which an individual may be unconscious or otherwise incompetent to give informed consent, but immediate intervention is not needed in order to prevent death because there is sufficient time to locate, and obtain consent from, a legally authorized representative. In those instances, it may be possible to delay treatment until a court appointed patient-advocate is arranged, the consent of a family member can be obtained, or some other procedure for a surrogate can be followed. There are also medical conditions that predictably occur in given identifiable subject populations. In those cases, it is possible to obtain advance consent before the intervention is required. In other cases, such as events that occur regularly in already hospitalized, acutely ill patients, the majority of subjects will have a family member or a legally authorized representative readily available to provide consent. In these instances, the research may, in accord with the provisions of the law of the jurisdiction, proceed without invoking a waiver of informed consent. In cases such as these, it will be inappropriate to invoke this exception.

The agency recognizes that there may be situations where research studies that would be conducted under § 50.24(a) may include a limited number of subjects for whom a representative is able to provide surrogate consent for the subject, and the treatment window may be such to permit such consent to be obtained. In anticipation of this possibility, the IRB will be required to have reviewed and approved an informed consent document in accord with § 56.109(b), so that surrogate consent can be obtained for those subjects.

Section 50.24(a)(5) describes four "additional protections" that would have to be provided for each protocol:

consultation with representatives of the communities from which the subjects will be drawn; public disclosure prior to the commencement of the study sufficient to describe the study and its risks and benefits; public disclosure of sufficient information following completion of the study to apprise the community and researchers of the study and its results; and the establishment of an independent data and safety monitoring board. In addition to these protections, the IRB should consider whether there are other appropriate additional protections that should be included to protect the rights and welfare of these subjects.

In order to provide for consultation with representatives of the communities from which the subjects will be drawn, and to supplement the information available for review by the IRB, all IRB's should consider, for example, having the clinical investigator or sponsor convene a public meeting in the community on the protocol; establishing a separate panel of members of the community from which the subjects will be drawn; including consultants to the IRB from the community from which the subjects will be drawn; enhancing the membership of the IRB by adding additional members who are not affiliated with the institution and are representative of the community; or developing some other mechanism to ensure community involvement and input into the IRB's decisionmaking process.

In order to provide for public disclosure, the IRB should consider how best to publicly disclose, prior to the commencement of the study, sufficient information to describe the study's risks and benefits, e.g., relevant information from the investigator's brochure or study protocol. Public disclosure following IRB review should be sufficient to disclose information concerning the IRB's resolution of issues and final decisions; this disclosure should provide community confidence in the role of the IRB and in its decisionmaking capability. Disclosure following completion of the study should provide sufficient information to the community about its results and sufficient information to researchers, which would include the underlying data, to be able to assess the results of the study.

The agency recognizes that the level of disclosure to representatives of the community and to researchers that would be required by § 50.24(a)(5) would require sponsors to disclose information about an investigation which they might not otherwise publicly disclose. FDA would require sponsors to provide copies to FDA of the publicly disclosed information for any investigation which proposes an exemption from the informed consent requirement. The agency believes that by disclosing the information described in this paragraph, the community will better understand the nature of the research and the rights and welfare of subjects will be better protected. By broadly sharing the results of the research with the scientific community, there may be less need to replicate the research; therefore, fewer subjects may be needed to obtain the same level of scientific knowledge and to advance emergency medicine.

Requiring an independent data and safety monitoring board would help ensure that if it becomes clear that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. For multi-center studies, the agency generally would expect the sponsor of the research, rather than the IRB, to establish the independent data and safety monitoring board. By "independent," the agency intends that the board be composed solely of individuals who have no financial interest in the outcome of the study, and who have not been involved in the design or conduct of the study. Section 56.111(a)(6) currently requires the IRB to determine that, where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. As discussed in the preamble to the January 27, 1981, regulations, in response to comments questioning the meaning of § 56.111(a)(6) and requesting guidelines for determining at what point in each experiment one treatment is shown to be safer and more effective than alternative treatments or no treatments, FDA responded:

> This [data monitoring] procedure might be an appropriate requirement in large scale clinical trials or in studies with a high degree of risk. The IRB may require the use of data safety monitoring boards in order to meet the requirements of this provision. Thus, if it becomes clear that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. This provision matches the HHS requirement * * *. IRB's generally will not have the scientific competence to make such a judgement [at what point in each experiment one treatment is shown to be safer and more effective than alternate treatments or no treatment]. The determination whether and at what point in an investigation a test article has been shown to be safe and effective in accordance with the requirements of the act is a determination that must be made by the investigator, the sponsor, and, ultimately, FDA.
> (46 FR 2869, January 27, 1981)

Section 50.24(b) describes a hierarchy of persons who should be informed of the subject's inclusion in the study, about the details of the study, and that the subject can discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The hierarchy is, first, the subject; if the subject remains incapacitated, then a legally authorized representative of the subject; if the representative is not available, a member of the subject's family is to be informed. The agency has included the phrase "without penalty or loss of benefits to which the subject is otherwise entitled" to ensure, in part, that a subject who is withdrawn from a study is provided with appropriate alternative medical care consistent with that person's medical condition.

The definition of "family members" in § 50.3(n) was taken from the Federal Government's Office of Personnel Management's final rule which relates, in part, to the use of sick leave to care for family members. That rule implements the Federal Employees Friendly Family Leave Act (Pub. L. 103-388), and was published in the **Federal Register** of December 2, 1994 (59 FR 62266). The definition has been modified by the phrase "legally competent" to acknowledge that family members must be not only of legal age, but also possess appropriate mental capacity, to have this information meaningfully conveyed to them.

F. Preemptive Effect

In developing these proposed rules, FDA considered whether there were existing State or local legal requirements governing informed consent that might limit or preclude participation in research in circumstances that otherwise could be authorized by IRB's acting in accord with these proposed rules. FDA believes that it is important that informed consent requirements governing this type of research be nationally uniform, particularly in light of the current confusion created in the research community by differing Federal regulations. FDA recognizes, however, that the existing Federal Policy for the Protection of Human Subjects, which governs much of this type of research, currently provides that it does not affect any State or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects. Accordingly, FDA specifically invites comment on whether there are existing State or local legal requirements that might limit or preclude participation in research in circumstances that otherwise could be

authorized by IRB's acting in accord with these proposed rules and whether any such requirements should be preempted by Federal requirements.

VIII. Effective Date

FDA is proposing to make these regulations effective on the date of publication of the final rule in the **Federal Register** because of the urgent need to permit emergency research to proceed. The agency believes that it is in the public interest to have a final rule in place as quickly as possible. By permitting certain controlled clinical trials to be conducted with the involvement of human subjects who are confronted by a life-threatening condition and who are also unable to give informed consent because of that condition, the agency expects to provide individual access to potentially beneficial treatment. The agency also expects that research to result in advancement and improvement of therapies used in emergency medicine situations that currently have poor clinical outcome. As a result of this rule, many individuals confronted by life-threatening situations will benefit immediately. Survival of these individuals may be enhanced by their participation in controlled trials. Therefore, FDA tentatively concludes that there is good cause to dispense with the normal 30-day period between publication of a final rule and its effective date.

IX. Request for Comments

Interested persons may, on or before November 6, 1995 submit to the Dockets Management Branch (address above) written comments regarding this proposal. Comments are also solicited regarding the need for Federal preemption (see sections VII.F. and XI.B. of this document) and information collection requirements subject to Office of Management and Budget (OMB) approval under the Paperwork Reduction Act of 1995 (see section XIII. of this document). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Comments on information collection requirements should be directed to FDA's Dockets Management Branch (address above) and to OMB's Office of Information and Regulatory Affairs (addressed below in section XIII. of this document).

FDA believes that a comment period greater than 45 days would be contrary to the public interest for the reasons given above. In addition, FDA is taking this action in response to the congressional hearing, the Consensus Conference, FDA/NIH Public Forum, and to public and professional concerns that not all of what has become standard and accepted medical therapy for use in acute or resuscitation care has been subjected to controlled clinical trials to establish its safety or effectiveness.

Currently, there are some investigations ongoing involving life-threatening conditions which enroll only subjects able to consent; other investigations are on hold pending issuance of this regulation. In those trials that are ongoing, accrual of subjects is exceedingly slow. Further delay could cause sponsors and funding institutions to cease support of such research, resulting in the research being stopped before sufficient data is gathered to demonstrate efficacy. FDA believes that extending the comment period would delay implementation of this rule and would result in the cessation of some of these studies or in the diversion of emergency research resources to other activities. As a result, potential subjects would be deprived of the opportunity to obtain potentially life-saving treatment. In addition, society would suffer as a result of this discontinuity in research by not being able to determine the effectiveness of potentially life-saving therapies.

Because of these public health concerns, FDA does not intend to extend the comment period beyond that date. Also, the agency is advising that it may not be able to consider any comments received at the Dockets Management Branch after the close of business on November 6, 1995. Although FDA is providing 45 days, rather than 90 days, for comments on this subject through the routine notice and comment procedures, it has received much input through the various conferences and congressional hearings discussed above and in correspondence. This input has come from IRB's, sponsors, investigators, ethicists, patient groups, etc.

The agency considered whether a reinterpretation of its existing regulations would meet the needs of persons in life-threatening situations and the research community. It concluded against such a reinterpretation for a number of reasons, including: it would not make the FDA regulations and the HHS regulations congruent; it would not provide prospective protections to subjects participating in such research; it would be difficult if not impossible to enforce additional safeguards that the agency believes are essential to protect subjects involved in such research activities; and it would not adequately eliminate the confusion that currently exists within the research community as to the standards that must be applied to this research. The sole benefit of a reinterpretation of existing regulations would be to permit this limited class of research to move forward quickly, rather than delaying until a new regulation could be written. The agency has, thus, placed priority on developing this proposed regulation in order to permit the ethical conduct of a limited class of emergency research.

X. 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.

XI. Executive Orders

A. Executive Order 12606: The Family

Executive Order 12606 directs Federal agencies to determine whether policies and regulations may have a significant impact on family formation, maintenance, and general well-being. FDA has analyzed this proposed rule in accordance with Executive Order 12606, and has determined that it has no potential negative impact on family formation, maintenance, and general well-being.

FDA has determined that this rule will not affect the stability of the family, and particularly, the marital commitment. It will not have any significant impact on family earnings. The proposed rule would not erode the parental authority and rights in the education, nurture, and supervision of children.

B. Executive Order 12612: Federalism

Executive Order 12612 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant effect on federalism. Using the criteria and principles set forth in the order, FDA has considered the proposed rule's impact on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government. FDA concludes that this proposal is consistent with the principles set forth in Executive Order 12612.

Executive Order 12612 states that agencies formulating and implementing

policies are to be guided by certain federalism principles. Section 2 of Executive Order 12612 enumerates fundamental federalism principles. Section 3 states that, in addition to these fundamental principles, executive departments and agencies shall adhere, to the extent permitted by law, to certain listed criteria when formulating and implementing policies that have federalism implications. Section 4 lists special requirements for preemption.

Section 4 of Executive Order 12612 states that an executive department or agency foreseeing the possibility of a conflict between State law and federally protected interests within its area of regulatory responsibility is to consult with States in an effort to avoid such conflict. Section 4 also states that an executive department or agency proposing to act through rulemaking to preempt State law is to provide all affected States notice and opportunity for appropriate participation in the proceedings. As required by the Executive Order, States have, through this notice of proposed rulemaking, an opportunity to raise the possibility of conflicts and to participate in the proceedings (section 4(d) and (e)). Consistent with Executive Order 12612, FDA requests information and comments from interested parties, including but not limited to State and local authorities, on these issues of federalism.

XII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–395). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule is a deregulatory action insofar as it will permit research to proceed which could not proceed under existing regulations, and because relatively few research projects will need to meet the requirements of this rule, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

XIII. Paperwork Reduction Act of 1995

This proposed rule contains only information collection requirements which are subject to review by the OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104–13), and which are already approved under Protection of Human Subjects—Recordkeeping Requirements for Institutional Review Boards, part 56 under OMB Control No. 0910–0130; Investigational New Drug Application under OMB Control No. 0910–0014; and Investigational Devices Exemption Reports and Records, part 812 under OMB Control No. 0910–0078. Modifications to these approved information collection requirements are underway.

For Protection of Human Subjects—Recordkeeping Requirements for Institutional Review Boards (IRB) under OMB Control No. 0910–0130, FDA has calculated the existing recordkeeping burden on IRB's based on the estimated number of IRB's and the estimated annual number of hours each IRB spends in recordkeeping activities. FDA does not believe that this rule will increase the number of IRB's. However, the agency estimates that the number of hours for recordkeeping related to studies which propose to invoke this exception from informed consent will increase for an estimated 200 IRB's by 5 annual hours per record-keeper. This will change the estimated recordkeeper burden from 65 to 70 hours annually.

The newly redesignated and revised § 56.109(e) proposes to require that an IRB notify in writing 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. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

For Investigational New Drug Application under OMB Control No. 0910–0014, the agency estimates that sponsors will submit an average of 20 studies a year, with an average of 20 clinical investigators each, that propose to invoke this exception from informed consent. Currently, the agency estimates the reporting requirements contained in part 312 to average 123.34 hours per respondent annually. FDA estimates that respondents will increase by 400 annually, resulting in an increase of 49,336 hours over that currently estimated. The reporting burden for respondents will, as a result, increase from an estimated 3,926,308 hours annually to 3,975,644 hours annually.

New § 312.54(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the trial or a substantially equivalent trial, and other IRB's that are asked to review the trial or a substantially equivalent trial. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

For recordkeeping, the agency estimated that an average of 165.13 hours were spent per respondent. For the estimated additional 400 recordkeeping respondents invoking this rule, this would result in approximately 66,072 hours annually. The recordkeeping burden for respondents will, as a result, increase from an estimated 2,244,090 hours annually to 2,310,162 hours annually.

For Investigational Devices Exemption Reports and Records under OMB Control No. 0910–0078, the agency estimates that 10 studies proposing to invoke this exception will be submitted to the agency annually. The number of studies upon which the current paperwork reporting burden is estimated may, therefore, increase from 244 original submissions to 254 original submissions, increasing the number of hours by 800 for respondents (estimated at 80 hours per submission), from a total of 19,520 to 20,320 hours annually.

New § 812.47(b) proposes to require the sponsor to provide information when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. This information is to be provided promptly in writing to FDA, investigators who are asked to participate in the trial or a substantially equivalent trial, and other IRB's that are asked to review the trial or a substantially equivalent trial. In accord with the Paperwork Reduction Act of 1995, this proposal discloses the agency's intent to require this third party notification.

The number of recordkeepers is currently estimated at 700; this number is not expected to change. The estimated number of annual hours for recordkeeping requirements is expected to increase by 100 hours. The agency had estimated that original submissions

require 10 hours annually of recordkeeping per submission; recordkeeping related to protocols invoking this rule are expected to increase the submissions from 244 to a total of 254.

As required by section 3507(d) of the Paperwork Reduction Act of 1995, FDA has submitted a copy of this proposed rule to OMB for its review of these previously approved information collection requirements. The agency solicits comments on the information collection requirements in order to: (1) Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility; (2) evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) enhance the quality, utility, and clarity of the information to be collected; and (4) minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses. Organizations and individuals desiring to submit comments on the information collection requirements should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, rm. 10235, New Executive Office Bldg., 725 17th Street, N.W., Washington, DC 20503, Attention: Desk Officer for FDA.

XIV. Conforming Amendments

This proposed rule would necessitate a number of changes to the regulations for human drugs, biologics, devices, and institutional review boards so that those regulations are consistent with this rule.

A. Amendments to Regulations for IRB's

FDA is proposing to amend § 56.109(c) to expressly recognize that IRB's may approve studies for which informed consent is not obtained when the requirements in § 50.24 are met. FDA is also proposing to amend § 56.109 to specify in the IRB regulations the requirement to notify sponsors when an IRB determines it cannot approve such studies and to notify sponsors when public disclosure of these studies has occurred. In addition, FDA is proposing to revise § 56.111 to reference the IRB's need to find that the criteria set forth in § 50.24 are met before approving investigations involving an exception from informed consent under § 50.24.

B. Amendments to Regulations for Human Drug Products

The proposed amendment to § 312.2(b) (21 CFR 312.2(b)) makes clear that these studies are not exempt from the requirements of part 312 (21 CFR part 312). Proposed § 312.20(a) and the amendments to § 312.30 would codify in the IND regulations the requirement for a separate IND for studies under § 50.24. Proposed new § 312.23(f) contains the requirement referenced in § 50.24(d) that sponsors prominently identify these studies in separate IND's. FDA is proposing to add new § 312.54 to specify the need for sponsors to actively monitor the progress of proposed investigations so that appropriate public disclosure can occur and so that other IRB's, investigators, and FDA are notified of an IRB determination that it cannot approve the investigation. Section 312.60 would be amended to reference the exception from informed consent in § 50.24. The amendment to § 314.430(d) (21 CFR 314.430(d)) would acknowledge that studies involving § 50.24 will not proceed without public discussion. Section 314.430(d) would be amended to codify that sponsors identify the information publicly disclosed.

C. Amendment to Biologics Regulations

FDA is proposing to amend 21 CFR 601.51(d) for the reasons set forth above for § 314.430(d).

D. Amendment to Device Regulations

FDA is proposing to amend §§ 812.20 and 812.35(a) (21 CFR 812.20 and 812.35(a) to codify in the IDE regulations the requirement for filing a separate IDE for studies under § 50.24. Section 812.20(b)(13) would be amended to codify the need to clearly identify in the IDE submission that the study involves an exception from informed consent under § 50.24. The amendment to § 812.38(b)(2) would acknowledge that studies involving § 50.24 will not proceed without public discussion. Section 812.38(b) would be amended to codify that sponsors identify the information publicly disclosed.

New § 812.47 would specify the need for the sponsor to actively monitor proposed investigations so that appropriate public disclosure can occur and so that other IRB's, investigators, and FDA are notified of an IRB determination that it cannot approve the investigation. FDA is proposing to amend 814.9(d) (21 CFR 814.9(d)) to codify the need for sponsors to identify information publicly disclosed consistent with the requirements of § 50.24(a)(5)(ii) and (a)(5)(iii).

XV. References

The following information has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Prentice, E. D., et al., "IRB Review of a Phase II Randomized Clinical Trial Involving Incompetent Patients Suffering from Severe Closed Head Injury," *IRB A Review of Human Subjects Research*, 15:1–7, 1993.

2. Prentice, E. D., et al., "An Update on the PEG–SOD Study Involving Incompetent Subjects: FDA Permits an Exception to Informed Consent Requirements," *IRB A Review of Human Subjects Research*, 16:16–18, 1994.

3. Fost N., and J. A. Robertson, "Deferring Consent with Incompetent Patients in an Intensive Care Unit," *IRB Review of Human Subjects Research*, 2:5–6, 1980.

4. Beauchamp, T. L., "Commentary: The Ambiguities of 'Deferred Consent'," *IRB Review of Human Subjects Research*, 2:6–9, 1980.

5. Levine, R. J., "Commentary: Deferred Consent," *Controlled Clinical Trials*, 12:546–550, 1991.

6. Olson, C. M., "Editorial: The Letter or the Spirit: Consent for Research in CPR," *Journal of the American Medical Association*, 271:1445–1447, 1994.

7. Abramson, N. S., and P. Safar, "Deferred Consent: Use in Clinical Resuscitation Research," *Annals of Emergency Medicine*, 19:781–784, 1990.

8. "Informed Consent—Legally Effective and Prospectively Obtained," OPRR Reports-Human Subject Protections, Number 93–3, 1993.

9. Jane, J. A., June 28, 1993, letter to D. A. Kessler and September 14, 1993, response.

10. Herr, D. L., July 23, 1993, letter to D. A. Kessler and September 14, 1993, response.

11. Binder, L. S., and M. H. Biros, July 23, 1993, letter to D. A. Kessler and September 14, 1993, response.

12. Zitnay, G. A., June 22, 1993, letter to D. A. Kessler and September 14, 1993, response.

13. Abramson, N. S., and P. Safar, "Response to Commentary," *Controlled Clinical Trials*, 12:551–552, 1991.

14. Parrillo, J. E., "Special Article: Research in critical care medicine: Present status of critical care investigation," *Critical Care Medicine*, 19:569–577, 1991.

15. Halperin, H. R., et al., "A Preliminary Study of Cardiopulmonary Resuscitation by Circumferential Compression of the Chest with Use of a Pneumatic Vest," *New England Journal of Medicine*, 329:762–768, 1993.

16. Cohen, T. J., et al., "A Comparison of Active Compression-Decompression Cardiopulmonary Resuscitation with Standard Cardiopulmonary Resuscitation for Cardiac Arrests Occurring in the Hospital," *New England Journal of Medicine*, 329:1918–1921, 1993.

17. Lurie, K. G., et al., "Evaluation of Active Compression-Decompression CPR in Victims of Out-of-Hospital Cardiac Arrest." *Journal of the American Medical Association*. 271:1405–1411, 1994.

18. Schwab, T. M., "A Randomized Clinical Trial of Active Compression-Decompression CPR vs Standard CPR in Out-of-Hospital Cardiac Arrest in Two Cities." *Journal of the American Medical Association*.273:1261–1268, 1995.

19. Olson, C. M., "Editorial: Plungers and Polemics: Active Compression-Decompression CPR and Federal Policy." *Journal of the American Medical Association*. 273:1299–1300, 1995.

20. Levine, R. J., "Editorial: Research in Emergency Situations; The Role of Deferred Consent," *Journal of the American Medical Association*, 273:1300–1302, 1995.

21. Marwick, C., "Research in Emergency Circumstances," *Journal of the American Medical Association*, 273:687–688, 1995.

22. "Informed Consent in Emergency Research." Consensus from the Coalition Conference of Acute Resuscitation and Critical Care Researchers, 1994.

23. "Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," transcript of January 9, 1995.

24. "Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," transcript of January 10, 1995.

25. "Report of the Public Forum on Informed Consent in Clinical Research Conducted in Emergency Circumstances," FDA and NIH, May 1995.

26. "Problems in Securing Informed Consent of Subjects in Experimental trials of Unapproved Drugs and Devices," Hearing before the Subcommittee on Regulation, Business Opportunities, and Technology of the Committee on Small Business, House of Representatives, Washington, DC, Serial No. 103–85, 1994.

27. Miller, B. L., "Philosophical, ethical, and legal aspects of resuscitation medicine," *Critical Care Medicine*, 16:1059–1062, 1988.

28. Miller, B. L., "The Ethics of Cardiac Arrest Research," *Annals of Emergency Medicine*, 22–118–124, 1993.

29. "Waiver of Informed Consent: A Critical Issue for Improving Treatment of Emergent Medical Conditions," North American Society of Pacing and Electrophysiology Government Relations Committee Position Statement, Testimony presented at FDA/NIH Public Forum, 1995.

30. Wears, R. L., Written testimony presented at FDA/NIH Public Forum, 1995.

31. McCarthy, C. R., "To Be or Not to Be: Waiving Informed Consent in Emergency Research," *Kennedy Institute of Ethics Journal*, 5:155–162, 1995.

32. "Implementing Human Research Regulations: Second Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and of their Implementation, for the Protection of Human Subjects," President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983.

33. Fost, N. C., "Part 3: Human Subjects in Cardiopulmonary Resuscitation Research," in "Ethics in Emergency Medicine." Edited by Iserson, K. V., et al., Williams & Wilkins, Baltimore, pp. 77–81, 1986.

34. Sprung, C. L., and B. J. Winick, "Informed Consent in Theory and Practice: Legal and Medical Perspectives on the Informed Consent Doctrine and a Proposed Reconceptualization," *Critical Care Medicine*, 17:1346–1354, 1989.

List of Subjects

21 CFR Part 50

Informed consent, Prisoners, Reporting and recordkeeping requirements, Research, Safety.

21 CFR Part 56

Human research subjects, Reporting and Recordkeeping requirements, Safety.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

21 CFR Part 814

Administrative practice and procedure, Confidential business information, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 50, 56, 312, 314, 601, 812, and 814 be 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, 721, 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, 379e, 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 adding a new paragraph (n) to read as follows:

§ 50.3 Definitions.

* * * * *

(n) *Family members* means the following legally competent persons: Spouses; parents; children (including adopted children); brothers, sisters and their spouses; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

3. Section 50.24 is added to subpart B to read as follows:

§ 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 be obtained if the IRB (with a concurring licensed physician member or consultant) 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 trials, is necessary to determine what particular intervention is most beneficial.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give consent as a result of their medical condition; and

(ii) The intervention under study must be administered before consent from legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for the research because the emergence of the condition to be studied cannot be predicted reliably in particular individuals.

(3) The opportunity for the subjects to participate in the research is in the interest of the subjects because:

(i) A life-threatening situation necessitates intervention, and

(ii) The risk of the investigation is reasonable in light of what is known about the medical condition and the risks and benefits of current therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The research could not practicably be carried out without the waiver.

(5) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (which may include consultation carried out by the IRB itself) with representatives of the

communities from which the subjects will be drawn;

(ii) Public disclosure prior to the commencement of the study sufficient to describe the study and its risks and benefits;

(iii) Public disclosure of sufficient information following completion of the study to apprise the community and researchers of the study and its results; and

(iv) The establishment of an independent data and safety monitoring board.

(6) The IRB has reviewed and approved an informed consent document for use with subjects or legal representatives in situations in which obtaining such consent may be feasible for some subjects.

(b) When possible and at the earliest possible 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) will be informed of the subject's inclusion in the research study, the details of the research study, and that 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) may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraphs (d) and (e) of this section are to be retained by the IRB for at least 3 years after completion of the research, 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 an investigational new drug application (IND) or investigational device exemption (IDE). FDA requires clear identification of protocols that would include subjects who are unable to consent, and submission of those protocols in a separate IND/IDE (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 supplemental applications under §§ 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve this research because the research 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 in writing to the sponsor of the research. The sponsor of the research must share this information with FDA. researchers/clinical investigators who are asked to participate in this or a substantially equivalent trial, and to other IRB's which are asked to review this or a substantially equivalent clinical trial.

PART 56—INSTITUTIONAL REVIEW BOARDS

4. 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, 721, 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, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C 216, 241, 262, 263b–263n).

5. Section 56.109 is amended by revising paragraph (c), by redesignating paragraphs (d) and (e) as paragraphs (e) and (f), by adding a new sentence to the end of newly redesignated paragraph (e), and by adding new paragraphs (d) and (g) to read as follows:

§ 56.109 IRB review of research.

* * * * *

(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, the IRB may required the investigator to provide subjects with a written statement regarding the research.

(e) * * * For studies involving an exception to informed consent under § 50.24 of this chapter, an IRB shall notify in writing 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.

* * * * *

(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)(5)(ii) and (a)(5)(iii). The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. The sponsor shall provide copies of the information disclosed to FDA.

6. Section 56.111 is amended by adding new paragraph (c) to read as follows:

§ 56.111 Criteria for IRB approval of research.

* * * * *

(c) When the research involves an exception from informed consent for emergency research under § 50.24 of this chapter, the IRB finds and documents that the safeguards set forth in § 50.24 are included.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

7. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C 321, 331, 351, 352, 353, 355, 356, 357, 371); sec 351 of the Public Health Service Act (42 U.S.C. 262).

8. Section 312.2 is amended by adding pragraph (b)(6) to read as follows:

§ 312.2 Applicability.

* * * * *

(b) * * *

(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

* * * * *

9. Section 312.20 is amended by adding paragraph (c) to read as follows:

§ 312.20 Requirements for an IND.

* * * * *

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter.

10. Section 312.23 is amended by adding paragraph (f) to read as follows:

§ 312.23 IND content and format.

* * * * *

(f) If the investigation involves an exception from informed consent under § 50.24 of this chapter, prominent

identification on the cover sheet that the investigation is subject to the requirements in § 50.24.

11. Section 312.30 is amended by adding a new sentence to the end of the introductory text to read as follows:

§ 312.30 Protocol amendments.

* * * Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

* * * * *

12. New section 312.54 is added to subpart D to read as follows:

§ 312.54 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all proposed investigations involving an exception from informed consent under § 50.24 of this chapter. The sponsor shall determine when the public disclosures required by § 50.24(a)(5)(ii) and (a)(5)(iii) of this chapter of the proposed investigation have occurred and promptly shall submit to the IND file and to Dockets Management Branch copies of the information that was disclosed.

(b) The sponsor also shall monitor such proposed investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA. investigators who are asked to participate in this or a substantially equivalent trial, and other IRB's that are asked to review this or a substantially equivalent trial.

13. Section 312.60 is amended by revising the second and third sentences in the text as follows:

§ 312.60 General responsibilities of investigators.

* * * An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in § 50.23 or § 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

14. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

15. Section 314.430 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 314.430 Availability for public disclosure of data and information in an application or abbreviated application.

* * * * *

(d)* * * For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IND file and to Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

PART 601—LICENSING

16. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263).

17. Section 601.51 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 601.51 Confidentiality of data and information in applications for establishment and product licenses.

* * * * *

(d) * * * For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IND file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

18. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 702, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C 216, 241, 262, 263b–263n).

19. Section 812.20 is amended by revising paragraph (a)(1) and adding paragraph (a)(4) to read as follows:

§ 812.20 Application.

(a) *Submission.* (1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under § 50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.

* * * * *

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter, and

(ii) If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24.

* * * * *

20. Section 812.35 is amended by adding a sentence to the end of paragraph (a) to read as follows:

§ 812.35 Supplemental applications.

(a) * * * Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IDE for such investigation.

* * * * *

21. Section 812.38 is amended by adding two sentences to the end of paragraph (b)(2) to read as follows:

§ 812.38 Confidentiality of data and information.

* * * * *

(b) * * *

(2) * * * If a device is subject to an investigation that involves an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information that has been publicly disclosed under § 50.24(a)(5)((ii) and (a)(5)(iii) to the IDE file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

22. New section 812.47 is added to subpart C to read as follows:

§ 812.47 Emergency research under § 50.24 of this chapter.

(a) The sponsor shall monitor the progress of all proposed investigations involving an exception from informed consent under § 50.24 of this chapter. The sponsor shall determine when the public disclosures under § 50.24(a)(5)(ii) and (a)(5)(iii) of this chapter of the proposed investigation have occurred. The sponsor promptly shall submit copies of the information that has been publicly disclosed to the IDE file and also to the Dockets Management Branch.

(b) The sponsor also shall monitor such studies to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in § 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent trial, and other IRB's that are asked to review this or a substantially equivalent trial.

PART 814—PREMARKET APPROVAL OF MEDICAL DEVICES

23. The authority citation for 21 CFR part 814 continues to read as follows:

Authority: Secs. 501, 502, 503, 510, 513–520, 701, 702, 703, 704, 705, 708, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 353, 360, 360c–360j, 371, 372, 373, 374, 375, 379, 379e, 381).

24. Section 814.9 is amended by adding two sentences to the end of paragraph (d) to read as follows:

§ 814.9 Confidentiality of data and information in a premarket approval application (PMA) file.

* * * * *

(d)* * * For applications concerning investigations involving an exception from informed consent under § 50.24 of this chapter, sponsors are required to submit copies of information publicly disclosed under § 50.24(a)(5)(ii) and (a)(5)(iii) to the IDE file and to the Dockets Management Branch. Copies of this information will be available to the public from the Dockets Management Branch.

* * * * *

Dated: August 31, 1995.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 95–23239 Filed 9–20–94; 8:45 am]

BILLING CODE 4160–01–F

E. Institutions With a National Institutes of Health (NIH) Multiple Project Assurance (MPA) as of May 10, 1995

Periodically, the Office for Protection from Research Risks (OPRR) updates this list and issues deactivation lists. Contact OPRR for the most current version of this list. (*See Chapter 14, Informational Contacts.*)

Assurance Number	State/Institution	City
	Alabama	
M1149	Alabama, University of, Birmingham, including.	Birmingham
M1149	Birmingham Regional Emergency Medical Services System	
M1149	Center for Aging	
M1149	Civitan International Research Center	
M1149	Lister Hill Library of the Health Sciences	
M1149	Mervyn H. Sterne Library	
M1149	Schools: Arts & Humanities; Business;	
M1149	Education; Engineering; Graduate School;	
M1149	Health Related Professions (Dentistry,	
M1149	Medicine, Nursing, Optometry,	
M1149	Public Health, Social & Behavioral Sciences);	
M1149	Natural Sciences & Mathematics	
M1149	University of Alabama Hospital	
M1074	Alabama, University of	Tuscaloosa
M1223	South Alabama, University of, including	Mobile
M1223	the Medical Center	
	Arizona	
M1108	Arizona State University	Tempe
M1233	Arizona, University of, including University Medical Center.	Tucson
M1435	including Barrow Neurological Institute	
M1006	Mayo Clinic Scottsdale/Mayo Foundation, MN	Scottsdale
M1006	Mayo Clinic Jacksonville, FL	
M1435	St. Joseph's Hospital and Medical Center, ...	Phoenix
M1493	Indian Health Service	Tucson
	Arkansas	
M1451	Arkansas, University of, Medical Center	Little Rock
	California	
M1336-XM	American Institutes for Research in	Palo Alto
M1336-XM	Behavioral Sciences (Headquarters—DC)	
M1043	Beckman Research Institute of the City of Hope	Duarte
M1043	National Medical Center	

Assurance Number	State/Institution	City
M1329	California Institute of Technology, including	Pasadena
M1329	Jet Propulsion Lab	
M1179	California Pacific Medical Center, including	San Francisco
M1179	ALS & Neuromuscular Research Center	
M1179	Garden Sullivan Hospital	
M1179	Medical Research Institute—See separate item.	
M1179	Senior Services	
M1179	Visiting Nurses & Hospice of San Francisco	
M1400	California State Health and Welfare Agency	Sacramento
M1400	(all Departments)	
M1349	California, University of, Berkeley/	Berkeley
M1349	Lawrence Berkeley Laboratories	
M1325	California, University of, Davis/Western	Davis
M1325	Human Nutrition Research Center (USDA)	
M1305	California, University of, Irvine, including	Irvine
M1305	Community Clinic of Orange County	Santa Ana
M1305	Medical Center	Orange
M1305	North Orange County Community Clinic	Anaheim
M1127	California, University of, Los Angeles	Los Angeles
M1147	California, University of, Riverside	Riverside
M1274	California, University of, San Diego	La Jolla
M1169	California, University of, San Francisco, including	San Francisco
M1169	Ambulatory Care Center/Clinics	
M1169	Cancer Research Institute	
M1169	Cardiovascular Research Institute	
M1169	Francis I. Proctor Foundation for Research in	
M1169	Ophthalmology	
M1169	George Williams Hooper Foundation	
M1169	Hormone Research Laboratory	
M1169	Institute for Health and Aging	
M1169	Institute for Health Policy Studies	
M1169	Laboratory of Radiobiology and Environmental Health	
M1169	Langley Porter Psychiatric Institute	
M1169	Long Hospital	
M1169	Metabolic Research Institute	
M1169	Moffitt Hospital	
M1169	Reproductive Endocrinology Center	
M1244	California, University of, Santa Barbara	Santa Barbara
M1205-XM	California, University of, Santa Cruz	Santa Cruz
M1157	Cedars-Sinai Medical Center	Los Angeles
M1386	Charles R. Drew University of Medicine &	Los Angeles
M1386	Science, Martin Luther King, Jr. General Hospital	
M1477	Children's Hospital and Research Center	San Diego
M1068	Children's Hospital	Oakland
M1118	Children's Hospital of Los Angeles	Los Angeles
M1272	Children's Hospital (Stanford University)	Stanford

Assurance Number	State/Institution	City
M1043	City of Hope National Medical Center Beckman Research Inst. . . .	Duarte
M1372	Doheny Eye Foundation, Hospital and Institution/	Los Angeles
M1372	LA County/USC Medical Center	
M1474	East Bay Institute of Research & Education/VA—Pleasant Hill	
M1169	Francis Proctor Foundation–Research, Ophthalmology/	San Francisco
M1169	University of California, San Francisco	
M1175	Friends Medical Science Research Center, Inc.	Beverly Hills
M1175	(Headquarters: See Maryland.)	Tarzana
M1169	George Hooper Foundation/University of California, S.F.	San Francisco
M1294	Green Hospital of Scripps Clinic	La Jolla
M1301	Harbor—UCLA Medical Center: See Research and Educ. Inst. . .	Torrance
M1312	Kaiser Foundation Research Institute & Foundation Hospitals	Oakland
M1312	Northern California Region	
M1312	Hayward Medical Center—Hayward	
M1312	Martinez Medical Center—Martinez	
M1312	Oakland Medical Center—Oakland	
M1312	Redwood City Medical Center—Redwood	
M1312	Richmond Medical Center—Richmond	
M1312	Sacramento Medical Center—Sacramento	
M1312	San Francisco Medical Center—San Francisco	
M1312	San Rafael Medical Center—San Rafael	
M1312	Santa Clara Medical Center—Santa Clara	
M1312	Santa Rosa Medical Center—Santa Rosa	
M1312	Santa Teresa—San Jose	
M1312	South Sacramento Medical Center—Sacramento	
M1312	South San Francisco Medical Center—So. San Francisco	
M1312	Vallejo Medical Center—Vallejo	
M1312	Walnut Creek Medical Center—Walnut Creek	
M1312	Southern California Region	
M1312	Anaheim Medical Center—Anaheim	
M1312	Bellflower Medical Center—Bellflower	
M1312	El Cajon Hospital—El Cajon	
M1312	Fontana Medical Center—Fontana	
M1312	Harbor City Medical Center—Harbor City	
M1312	Los Angeles Medical Center—Los Angeles	
M1312	Panorama City Medical Area—Panorama City	
M1312	Riverside Medical Center—Riverside	
M1312	San Diego Medical Center—San Diego	
M1312	West Los Angeles Medical Center—W. Los Angeles	
M1312	Woodland Hills Medical Center—Woodland Hills	
M1179	Los Angeles County: See Los Angeles County items.	
M1383	La Jolla Cancer Research Foundation	La Jolla
M1169	Langley Porter Psychiatric Institute/	San Francisco
M1169	University of California, San Francisco	
M1349	Lawrence Berkeley Labs/University of California, Berkeley	Berkeley

Assurance Number	State/Institution	City
M1415-XB	Lawrence Livermore National Laboratory	Livermore
M1295	Loma Linda University, including	Loma Linda
M1295	the Medical Center & Community Hospital	Riverside
M1169	Long Hospital/University of California, San Francisco.	San Francisco
M1114	Los Amigos Research and Education Institute (formerly	Downey
M1114	Rancho Los Amigos Hospital & Professional Staff Association)	
M1372	Los Angeles County—University of Southern California	Los Angeles
M1372	Medical Center (including the Schools of	
M1372	Dentistry, Medicine, Nursing, and Pharmacy);	
M1372	Communicable Diseases Hospital; Doheny Eye Fdn./Hospital/Inst.;	
M1372	General Hospital; Pediatric Pavilion & Acute Unit &	
M1372	Cancer Center; Psychiatric Hospital; and the Campus	
M1372	Outpatient facilities as follows:	
M1372	Institute for Preventive Research—Alhambra	
M1372	Kenneth Norris Cancer Research Institute and Hospital	
M1372	USC Ambulatory Health Center	
M1372	USC Healthcare Consultation Center	
M1386	Los Angeles County King/Drew Medical Center, including	Los Angeles
M1386	the Medical School, the General Hospital, and	
M1386	the Professional Staff Association Foundation	
M1386	Martin Luther King Jr. General Hospital/	Los Angeles
M1386	Charles R. Drew University of Medicine & Science	
M1179	Medical Res. Inst. (California Pacific Med. Ctr.), including	San Francisco
M1179	Clinical Studies Center	
M1179	Geraldine Brush Cancer Research Institute (GBCRI)	
M1179	Heart Research Institute (HRI)	
M1179	Institute of Child Health & Human Development (ICHHD)	
M1179	Institute of Epidemiology & Behavioral Medicine (IEBM)	
M1179	Institute of General Medical Sciences	
M1179	Institute of Neurological Sciences (INS)	
M1179	Kuzzell Institute for Arthritis & Infectious Diseases	
M1373	Memorial Health Services (Parent Corporation), including	Long Beach
M1373	Long Beach Memorial Medical Center, including	
M1373	Memorial Hospital, Womens Hospital, Miller	
M1373	Children's Hospital, Memorial Heart Institute,	
M1373	and Memorial Cancer Institute	
M1373	Memorial Health Technologies	
M1373	Saddleback Memorial Medical Center	
M1419	Mental Research Institute	Palo Alto
M1169	Moffitt Hospital/University of California, San Francisco	San Francisco
M1380-XB	Northern California Cancer Center	Union City
M1508	Olive View, UCLA Education & Research Institute	Sylmar
M1489	Pacific Institute for Research & Evaluation	Walnut Creek
M1489	(also Maryland)	

Assurance Number	State/Institution	City
M1005-XB	Palo Alto Medical Foundation for Research, Health Care	Palo Alto
M1005-XB	& Education, including the Research Institute	
M1114	Rancho Los Amigos Hospital Professional	Downey
M1114	Staff Association—Renamed: See	
M1114	Los Amigos Research & Education Institute.	
M1031	Rand Corporation	Santa Monica
M1301	Research & Education Institute/Harbor—UCLA Medical Center	Torrance
M1022	Salk Institute	San Diego
M1436	San Diego State University	San Diego
M1204	San Francisco State University	San Francisco
M1165	San Jose State University	San Jose
M1020-XM	Scientific Analysis Corporation and	San Francisco
M1020-XM	the Institute for Scientific Analysis	
M1020-XM	(Performance Sites also in Berkeley and Alameda)	
M1294-XB	Scripps Clinic and Research Foundation, including	La Jolla
M1294-XB	Green Hospital and Scripps Research Institute (TSRI)	
M1179	Smith-Kettlewell Eye Research Institute	San Francisco
M1299	Southern California, University of	Los Angeles
M1299	(University Park campus)	
M1372	Southern California, University of: See also	Los Angeles
M1372	Los Angeles County—USC Medical Center.	
M1088	SRI International	Menlo Park
M1272	Stanford University	Stanford
M1179	University of the Pacific/School of Dentistry	San Francisco
M1274	Veterans Affairs, Dept. of, Medical Center and	San Diego
M1274	University of California, San Diego	
M1163	Veterans Affairs, Dept. of, Medical Center	Long Beach
M1474	Veterans Affairs, Northern California System	Pleasant Hill
M1474	of Clinics, including Berkeley, Martinez,	
M1474	Oakland, Redding, and Sacramento, and	
M1474	East Bay Institute of Research and Education	
M1292	Veterans Affairs, Dept. of, Medical Center	Sepulveda
M1087	Veterans Affairs, Dept. of, Medical Center West Los Angeles,	Los Angeles
M1087	including Wadsworth & Brentwood Divisions	
M1325	Western Human Nutrition Research Center (USDA)/	Davis
M1325	University of California, Davis	
M1158-XM	Wright Institute	Berkeley
	Colorado	
M1494	Children's Hospital	Denver
M1494	Colorado Consortium of Medical Institutes (CCMI)	Denver
M1494	Colorado Prevention Center (CCMI)	Denver
M1498	Colorado, State of, Dept. of Health	Denver
M1153-XB	Colorado State University	Fort Collins
M1144-XM	Colorado, University of	Boulder

Assurance Number	State/Institution	City
M1494	Colorado, University of, Health Science Center (CCMI)	Denver
M1494	University Hospital (CCMI)	
M1494	Denver Health and Hospitals (CCMI)	Denver
M1410	Denver, University of (Colorado Seminary), including	Denver
M1410	Denver Research Institute, Academic Research Center	
M1009	National Jewish Center for Immunology and	Denver
M1009	Respiratory Medicine	
M1494	Veterans Affairs, Dept. of, Medical Center (CCMI)	Denver
M1494	University Hospital (University of Colorado—CCMI)	Denver
	Connecticut	
M1057	Connecticut State Dept. of Health	Hartford
M1057	(all sections)	
M1023	Connecticut, University of	Storrs
M1345	Connecticut, University of, Health Center/	Farmington
M1345	VA Hospital–Newington	
M1421	Hartford Hospital	Hartford
M1470	Newington Children's Hospital Corporation, including	Newington
M1470	Child Development Center—sites in East Hartford, Newington,	
M1470	Stafford Springs, and West Hartford	
M1470	Newington Orthotic & Prosthetic Systems—	
M1470	Centers in East and West Hartford,	
M1470	New Haven, Newington,	
M1470	Norwalk, and Waterbury, CT; and Warwick, RI	
M1276	Saint Francis Hospital & Medical Center	Hartford
M1345	Veterans Affairs, Dept. of., Medical Center—Newington/	Newington
M1345	University of Connecticut Health Center	
M1437	Waterbury Hospital	Waterbury
M1452	Yale University	New Haven
	Delaware	
M1360	Delaware, University of	Newark
M1366	Medical Center of Delaware, Inc.	Wilmington
M1366	(formerly Wilmington Medical Center, Inc.)	
	District of Columbia	
M1336-XM	American Institutes for Research in the	Washington
M1336-XM	Behavioral Sciences (including sites in	
M1336-XM	Washington, D.C.; Palo Alto, California)	
M1228-XB	American National Red Cross/Headquarters: See Maryland.	Washington
M1066-XM	Catholic University of America	Washington
M1316	Children's Hospital National Medical Center	Washington
M1318-XM	Gallaudet University	Washington

Assurance Number	State/Institution	City
M1125	George Washington University	Washington
M1255	Georgetown University	Washington
M1102	Howard University and Howard University Hospital	Washington
M1454	Medlantic Research Institute, including	Washington
M1454	Washington Hospital Center, National Rehabilitation Hospital;	
M1454	Center for Ambulatory Surgery	
M1219	National Academy of Sciences, including	Washington
M1219	National Academy of Engineering, Institute of Medicine,	
M1219	and National Research Council	
M1408	Veterans Affairs, Dept. of, Medical Center	Washington
M1503	Walter Reed Army Medical Center	Washington
M1454	Washington Hospital Center: See Medlantic Research Fdn.	Washington
	Florida	
M1350	Florida State Department of Health and	Tallahassee
M1350	Rehabilitative Services	
M1339-XM	Florida State University	Tallahassee
M1266	Florida, University of/VA Medical Center, including	Gainesville
M1266	J. Hillis Miller and Health Center and	
M1266	Shands Teaching Hospital	
M1266	University of Florida Health Science Center	Jacksonville
M1196	Jackson Memorial Hospital/University of Miami	Miami
M1006	Mayo Clinic Jacksonville, including St. Luke's Hospital/	Jacksonville
M1006	Mayo Foundation, MN/Mayo Clinic Scottsdale, AZ	
M1101-XB	Miami Heart Research Institute	Miami Beach
M1196	Miami, University of	Coral Gables
M1196	Miami, University of/Jackson Mem. Hosp./VA Medical Center	Miami
M1196	Bascom Palmer Eye Institute	
M1196	Behavioral Medical Research Center	
M1196	University Hospital and Clinics	
M1124-XB	Mt. Sinai Medical Center of Greater Miami	Miami Beach
M1196	Papanicolaou Cancer Research Institute (University of Miami)	Miami
M1196	Public Health Trust of Dade County, including	Miami
M1196	Human Resources Health Center	
M1196	Jackson Memorial Hospital	
M1196	Jackson North Maternity Center	
M1196	Liberty City Health Center	
M1196	North Dade Health Center	
M1196	Perdue Medical Center	
M1284	South Florida, University of	Tampa
M1266	Veterans Affairs, Dept. of, Medical Center/Univ. of Florida	Gainesville
M1196	Veterans Affairs, Dept. of, Medical Center/Univ. of	Miami
M1196	Miami/Jackson Memorial Hospital	

Assurance Number	State/Institution	City
	Georgia	
M1141	Agency for Toxic Substances & Disease Registry	Atlanta
M1141	Centers for Disease Control and Prevention, PHS, including	Atlanta
M1141	National Center for Health Statistics	
M1141	(Hyattsville, MD, and Research Triangle Park, NC)	
M1346-XM	Emory University Graduate School of Arts and Sciences	Atlanta
M1426	Emory University Nell Hodgson Woodruff	Atlanta
M1426	School of Nursing	
M1426	Emory University Robert W. Woodruff Health	Atlanta
M1426	Sciences Center, including	
M1426	Crawford W. Long Memorial Hospital	
M1426	Emory University Hospital	
M1426	School of Medicine	
M1426	School of Nursing	
M1426	School of Public Health	
M1026	Georgia Dept. of Human Resources (all units)	Atlanta
M1395	Georgia Institute of Technology, including	Atlanta
M1395	Georgia Tech. Research Corporation	
M1395	and Georgia Tech. Research Institute	
M1047	Georgia, University of, and Research Foundation	Athens
M1312-XB	Kaiser Southeast Permanente Medical Group, Inc.	Atlanta
M1312-XB	(Medical Clinics)	
M1112	Medical Coll. of Georgia & Research Institute/VA Medical Center	Augusta
M1513	Morehouse School of Medicine	Atlanta
M1141	National Center for Health Statistics (CDC)	Atlanta
M1220	National Institute for Occupational Safety & Health	Atlanta
M1461-XB	University Hospital	Augusta
M1112	Veterans Affairs, Dept. of, Med. Ctr./Medical Coll. of Georgia	Augusta
	Hawaii	
M1217	Hawaii, University of, System, including	Honolulu
M1217	Hawaii Community College	
M1217	Honolulu Community College	
M1217	Kapiolani Community College	
M1217	Kauai Community College	
M1217	Leeward Community College	
M1217	Maui Community College	
M1217	University of Hawaii at Hilo	
M1217	University of Hawaii at Manoa	
M1217	West Oahu College	
M1217	Windward Community College	
M1312	Kaiser Foundation Hospitals (Hawaii Region)	Honolulu
M1312	Kaiser Permanente Medical Center—Honolulu	

Assurance Number	State/Institution	City
	Illinois	
M1365	American Dental Association and ADA Health Foundation	Chicago
M1365	and Paffenbarger Research Center (Gaithersburg, MD)	
M1264	Bernard Mitchell Hospital/University of Chicago	Chicago
M1264	Chicago Lying-In Hospital/University of Chicago	Chicago
M1236	Chicago Medical School of University of Health Sciences	North Chicago
M1264	Chicago, University of, Divisions of, including	Chicago
M1264	Biological Sciences, Pritzker School	
M1264	of Medicine, Social Sciences, School of Social	
M1264	Service Admin., and University of Chicago Hospital & Clinics:	
M1264	Bernard Mitchell Hospital	
M1264	Chicago Lying-In Hospital	
M1264	Louis A. Weiss Memorial Hospital	
M1264	Wyler Children's Hospital	
M1484	Children's Memorial Institute for	Chicago
M1484	Education & Research, including Children's Memorial Hospital	
M1321-XM	Choate Mental Health and Developmental Center	Anna
M1150	Cook County Hospital and Hektoen Institute	Chicago
M1396	Evanston Hospital Corporation, including	Evanston
M1396	Evanston Hospital & Glenbrook Hospital	
M1387	Foster G. McGraw Hospital (Loyola University Medical Center)	Maywood
M1014	Galen Hospital Illinois: See Michael Reese	
M1150	Hektoen Institute for Medical Research and	Chicago
M1150	Cook County Hospital	
M1279	Illinois State Psychiatric Institute	Chicago
M1095	Illinois, University of, at Chicago	Chicago
M1095	Illinois, University of, Medical Center, including	Chicago
M1095	Colleges of Nursing—Peoria,	
M1095	Rockford & Urbana-Champaign	
M1095	Illinois, University of, College of Medicine	Peoria
M1476	Illinois, University of, College of Medicine, Rockford	Rockford
M1004	Illinois, University of, all components	Urbana
M1004	at Urbana-Champaign	
M1264	Louis A. Weiss Memorial Hospital/University of Chicago	Chicago
M1387	Loyola University Medical Center, including	Maywood
M1387	Foster G. McGraw Hospital	
M1387	Graduate School–Medical Center	
M1387	Mulcahy Outpatient Center	
M1387	Oakbrook Terrace Medical Center	
M1387	Oncology Institute	
M1387	School of Nursing	
M1387	Stritch School of Medicine	
M1014	Michael Reese Hospital and Research and Education Fdn.	Chicago
M1413	Northern Illinois University	DeKalb
M1319	Northwestern Medical Faculty Foundation, including	Chicago

Assurance Number	State/Institution	City
M1319	Northwestern Memorial Hospital	Chicago
M1319	Northwestern University	Chicago
M1319	Northwestern University	Evanston
M1319	Rehabilitation Institute of Chicago	Chicago
M1385	Rush-Presbyterian—St. Luke's Medical Center	Chicago
M1042-XM	Southern Illinois University	Carbondale
M1137-XM	Southern Illinois University	Edwardsville
M1311	Southern Illinois University, School of Medicine	Springfield
M1236	University of Health Sciences, Chicago Medical School	North Chicago
M1472	Veterans Affairs, Dept. of,	Hines
M1472	Edward Hines Jr. Hospital	Hines
M1319	Veterans Affairs, Dept. of, Lakeside Hospital	Chicago
M1516	Veterans Affairs, Dept. of, Medical Center	North Chicago
M1264	Wyler Children's Hospital (University of Chicago)	Chicago
	Indiana	
M1167	Indiana University—Bloomington	Bloomington
M1167	Indiana University—East	Richmond
M1167	Indiana University—Kokomo	Kokomo
M1167	Indiana University—Northwest	Gary
M1167	Indiana University—South Bend	South Bend
M1167	Indiana University—Southeast	New Albany
M1167	Indiana University Hospital	Indianapolis
M1167	Indiana University—Purdue University, Columbus Center	Columbus
M1167	Indiana University—Purdue University	Indianapolis
M1167	J.W. Riley Hospital for Children (Indiana University)	Indianapolis
M1167	Krannert Institute of Cardiology (Indiana University)	Indianapolis
M1342	Methodist Hospital of Indiana, Inc.	Indianapolis
M1262-XM	Notre Dame, University of	Notre Dame
M1167	Oral Health Research Institute (Indiana University)	Indianapolis
M1162	Purdue University and Purdue Research Foundation	West Lafayette
	Iowa	
M1361	Iowa State University	Ames
M1080	Iowa, University of	Iowa City
	Kansas	
M1296	Kansas State University	Manhattan
M1234	Kansas, University of—Lawrence Campus	Lawrence
M1122	Kansas, University of, Medical Center and Hospitals	Kansas City
M1122	Kansas, University of, School of Medicine,	Wichita
M1122	School of Nursing & School of Allied Health	
M1432	Menninger Clinic	Topeka

Assurance Number	State/Institution	City
	Kentucky	
M1189	Humana Hospital (Humana of Virginia, Inc.)/	Louisville
M1189	University of Louisville	
M1324	Kentucky, University of, and Research Fdn./VA Hospital	Lexington
M1189	Kosair Children's Hospital (NKC Hospital, Inc.) University	Louisville
M1189	of Louisville	
M1189	Louisville, Univ. of, including Humana Hospital, Inc	Louisville
M1189	Kosair Children's Hospital, Norton Hospital	
M1189	Norton Hospital (NKC Hospital, Inc.)/Univ. of Louisville	Louisville
M1324	Veterans Affairs, Dept. of, Hospital/University	Lexington
M1324	of Kentucky	
	Louisiana	
M1046	Alton Ochsner Medical Foundation	New Orleans
M1128	Louisiana State University and A&M College/	Baton Rouge
M1128	Pennington Biomedical Research Center	
M1129-XM	Louisiana State University Agricultural Center	Baton Rouge
M1130	Louisiana State University Medical Center, including	New Orleans
M1130	Lions/LSU Eye Clinic; Schools of	
M1130	Allied Health Professions, Dentistry,	
M1130	Graduate Studies, Medicine and Nursing	
M1131-XB	Louisiana State University Medical Center—Shreveport	Shreveport
M1132-XM	Louisiana State University	Alexandria
M1135-XM	New Orleans, University of	New Orleans
M1128	Pennington Biomedical Research Center/LSU A&M	Baton Rouge
M1039-XM	Pinecrest State School	Pineville
M1260	Tulane University Medical Center	New Orleans
M1267-XM	Tulane University, Uptown Campus	New Orleans
	Maine	
M1353	Eastern Maine Medical Center	Bangor
M1197	Maine Medical Center, including Research Institute	Portland
	Maryland	
M1365	American Dental Association—Paffenbarger	Gaithersburg
M1365	Research Center	
M1228	American National Red Cross Biomedical Services,	Rockville
M1228	Holland Laboratory and Regional Blood Centers (HQ–D.C.)	
M1175	Friends Medical Science Research Center, Inc.	Baltimore
M1493	Indian Health Service	Rockville
M1140	Johns Hopkins Bayview Medical Center, and the following:	Baltimore
M1140	Addiction Research Center (NIDA)	
M1140	Bayview Research Groups (JHU School of Medicine)	
M1140	Gerontology Research Center (NIA)	

Assurance Number	State/Institution	City
M1091-XM	Johns Hopkins University Homewood Schools	Baltimore
M1090	Johns Hopkins University School of Hygiene and	Baltimore
M1090	Public Health	
M1011	Johns Hopkins University School of Medicine and	Baltimore
M1011	Johns Hopkins Hospital/Kennedy Krieger Institute for	
M1011	Handicapped Children, and STD Clinics at	
M1011	Druid Hill District & Eastern Health District	
M1011	Johns Hopkins University School of Nursing	Baltimore
M1011	Kennedy Krieger Institute/Johns Hopkins University	Baltimore
M1011	School of Medicine	
M1527-XB	Maryland Medical Research Institute	Baltimore
M1174	Maryland, University of, at Baltimore	Baltimore
M1265-XM	Maryland, University of, Baltimore County	Catonsville
M1362-XM	Maryland, University of, at College Park	College Park
M1141	National Center for Health Statistics, CDC	Hyattsville
M1141	(also North Carolina)	
M1515	National Naval Medical Center—Hospital Components only	Bethesda
M1515	under Sciences, Education & Training Command	
M1222-XB	NCI/Frederick Cancer Research & Dev. Center, including	Frederick
M1222-XB	ABL-Basic Research Program	
M1222-XB	Frederick Memorial Hospital	
M1222-XB	Sciences, Applications, International Corp. (SAIC)	
M1000	NIH, Clinical Center, all Institutes & Units	Bethesda
M1489	Pacific Institute for Research & Evaluation	Bethesda
M1489	(also California)	
M1338-XB	Sinai Hospital of Baltimore, Inc	Baltimore
M1441	U.S. Food & Drug Administration/PHS/HHS	Rockville
	Massachusetts	
M1310	Beth Israel Hospital	Boston
M1409	Boston City, Dept. of Health & Hospitals	Boston
M1409	Boston Specialty & Rehabilitation Hospital	
M1409	Codman Square Health Center	
M1409	Dorchester House Multi-Service Center	
M1409	East Boston Neighborhood Health Center	
M1409	Long Island Hospital	
M1409	South Boston Neighborhood Health Center	
M1409	Boston City Hospital: See Trustees of Health	Boston
M1428	Boston University, Charles River Campus	Boston
M1290	Boston University Medical Center	Boston
M1290	Boston University School of Graduate Dentistry	Boston
M1290	Boston University School of Medicine, including	Boston
M1290	School of Public Health	
M1416	Brandeis University, including Channing Lab	Waltham
M1049	Brigham and Women's Hospital	Boston

Assurance Number	State/Institution	City
M1271-XB	CBR Laboratories, Inc. (Center for Blood Research)	
M1271-XB	Center for Blood Research, Inc. & CBR Labs, Inc.	Boston
M1273	Children's Hospital Corporation, Inc.	Boston
M1034	Dana Farber Cancer Institute, Inc.	Boston
M1289	Deaconess Hospital	Boston
M1378	Eunice Kennedy Shriver Center for Mental Retardation	Waltham
M1352-XB	Eye Research Institute: See Schepens Eye Research Institute.	
M1024-XB	Forsyth Dental Center	Boston
M1240	Harvard Medical School, including School of Dental Medicine	Boston
M1084	Harvard University, Faculty of Arts and Science	Cambridge
M1208	Harvard University, School of Public Health, including	Boston
M1240	Harvard Institute for International Development	
M1286	Joslin Diabetes Center	Boston
M1288	Lahey Clinic Foundation and Lahey Clinic Medical Center	Burlington
M1417-XB	Lemuel Shattuck Hospital, Massachusetts Dept. of	Jamaica Plain
M1417	Public Health	
M1409	Long Island Hospital	Boston
M1243	Massachusetts Dept. of Mental Health	Boston
M1354-XB	Massachusetts Eye and Ear Infirmary	Boston
M1331	Massachusetts General Hospital, including	Boston
M1331	Bunker Hill Health Center—Charlestown	
M1331	Chelsea Health Center—Chelsea	
M1331	North End Community Health Center—Boston	
M1331	Revere Health Associates—Revere	
M1377	Massachusetts Institute of Technology/Whitehead	Cambridge
M1377	Institute for Biomedical Research	
M1431	Massachusetts Mental Health Center	Boston
M1431	Massachusetts Mental Health Research Corp.	Boston
M1003	Massachusetts, University of	Amherst
M1526	Massachusetts, University of	Boston
M1207	Massachusetts, University of, Medical School, including	Worcester
M1207	Family Practice Residency Program—Fitchburg	
M1409	Mattapan Hospital	Mattapan
M1287	McLean Hospital Corporation	Belmont
M1440	New England Medical Center Hospitals, including	Boston
M1440	Boston Dispensary	
M1440	Boston Floating Hospital	
M1440	Health Institute	
M1440	Kiwanis Pediatric Trauma Institute	
M1440	New England Eye Center	
M1440	NEMC Basic Research Corp., Inc.	
M1440	Tupper Research Institute	
M1504	New England Research Institute, Inc.	Watertown
M1298	North Charles Mental Health Research &	Cambridge
M1298	Training Fdn., including Cambridge Hosp. Dept. of Psychiatry	

Assurance Number	State/Institution	City
M1275	Northeastern University	Boston
M1352-XB	Schepens Eye Research Institute (was Eye Research Inst.)	Boston
M1460	St. Elizabeth's Hospital of Boston	Boston
M1409	Trustees (and Dept. of) Health & Hospitals, City of Boston,	Boston
M1409	including Boston City Hospital	
M1439	Tufts–New England Medical Center	Boston
M1440	Boston Dispensary	
M1440	Boston Floating Hospital	
M1440	Health Institute	
M1440	Kiwanis Pediatric Trauma Institute	
M1440	New England Eye Center	
M1440	NEMC Basic Research Corp., Inc.	
M1440	Tupper Research Institute	
M1438	Tufts University Health Sciences, including	Boston
M1438	Medical School, Dental School, Veterinary School,	
M1438	Sackler School of Graduate Biomedical Sciences	
M1328	Tufts University—Medford	Medford
M1290	University Hospital, Inc. (Boston University Medical School)	Boston
M1488	Veterans Affairs, Dept. of, Medical Center	Boston
M1377	Whitehead Institute/Massachusetts Institute of Technology	Cambridge
M1229	Worcester Foundation for Experimental Biology	Shrewsbury
	Michigan	
M1191	Henry Ford Health System	Detroit
M1341	Michigan Cancer Foundation	Detroit
M1320	Michigan Department of Public Health	Lansing
M1239	Michigan State University	East Lansing
M1184	Michigan, University of, and University	Ann Arbor
M1184	Hospital System, including Univ. Hospital (Adult General Hosp.),	
M1184	Taubman Health Care Center, Mott Children's Hosp.,	
M1184	Women's Hosp., Holden Perinatal Hosp., Turner Geriatric Center,	
M1184	Adult Psychiatric Hosp., Child and Adolescent Psychiatric Hosp.,	
M1184	and Kellogg Eye Center	
M1184	Michigan, University of	Dearborn
M1184	Michigan, University of	Flint
M1071	Oakland University	Rochester
M1201	Veterans Affairs, Dept. of, Medical Center—Ann Arbor	Ann Arbor
M1261	Wayne State University	Detroit
M1192-XM	Western Michigan University	Kalamazoo
M1482	William Beaumont Corporation and Hospital	Royal Oak
	Minnesota	
M1154	Hennepin County Medical Center/Minneapolis Medical	Minneapolis
M1154	Research Foundation and Hennepin Faculty Associates	

Assurance Number	State/Institution	City
M1006	Mayo Foundation Headquarters, including	Rochester
M1006	Co-signers.	
M1006	Mayo Clinic Jacksonville, FL, including St. Luke's Hospital	
M1006	Mayo Clinic Scottsdale, AZ	
M1006	Mayo Clinic (Headquarters) Rochester	
M1006	Rochester Methodist Hospital (Headquarters)	
M1006	St. Marys Hospital—Rochester	
M1154	Minneapolis Medical Res. Fdn./Hennepin County Med. Ctr.	Minneapolis
M1337	Minnesota, University of, Hormel Institute	Austin
M1337	Minnesota, University of	Crookston
M1337	Minnesota, University of	Duluth
M1337	Minnesota, University of	Minneapolis
M1337	Minnesota, University of	Morris
M1337	Minnesota, University of	St. Paul
M1337	Minnesota, University of Hospital & Medical Center	Minneapolis
M1160	Veterans Affairs, Dept. of, Medical Center	Minneapolis
	Mississippi	
M1237	Mississippi, University of (Main Campus)	University
M1045	Mississippi, University of, Medical Center	Jackson
	Missouri	
M1382	Jewish Hospital of St. Louis	St. Louis
M1412	Kirksville College of Osteopathic Medicine	Kirksville
M1051	Midwest Research Institute	Kansas City
M1502	Missouri, University of	Columbia
M1505	Missouri, University of, including Truman Medical Center and	Kansas City
M1505	Children's Mercy Hospital	
M1499	Missouri, University of	Rolla
M1497	Missouri, University of	St. Louis
M1119	St. Louis University, including all Centers,	St. Louis
M1119	Departments, Divisions, Offices, Programs, and Schools	
M1096-XB	Veterans Affairs, Dept. of, Medical Center	Kansas City
M1522	Veterans Affairs, Dept. of, Medical Center	St. Louis
M1397-XM	Washington University (except School of	St. Louis
M1397-XM	Medicine and Dentistry)	
M1123	Washington University School of Medicine	St. Louis
	Nebraska	
M1117	Creighton University	Omaha
M1218	Father Flanagan's Boys' Home	Boys Town
M1511	Nebraska, University of	Kearney
M1510	Nebraska, University of	Lincoln

Assurance Number	State/Institution	City
M1509	Nebraska, University of, including Medical Center	Omaha
M1478-XB	Veterans Affairs, Dept. of, Medical Center	Omaha
	Nevada	
M1164	Nevada, University of	Las Vegas
M1164	Nevada, University of	Reno
M1164	Sierra Biomedical Research Corp. (Univ. of Nevada)	Reno
M1164	Veterans Affairs, Dept. of, Ionnis A. Lougaris	Reno
M1164	Medical Center	
	New Hampshire	
M1520	Trustees of Dartmouth College, including	Hanover
M1520	College of Arts & Sciences	
M1520	Dartmouth Medical School	
M1520	Thayer School of Engineering	
M1520	Tuck Business School	
M1278	New Hampshire, University of	Durham
	New Jersey	
M1490	Center for Molecular Medicine and Immunology	Newark
M1069-XB	Coriell Institute for Medical Research (formerly	Camden
M1069-XB	Institute for Medical Research)	
M1418-XM	Educational Testing Service	Princeton
M1069-XB	Institute for Medical Research: See Coriell Institute.	Camden
M1002	Princeton University	Princeton
M1467	Robert Wood Johnson University Hospital	Piscataway
M1467	(UMDNJ-RWJ Medical School)	
M1370	Rutgers, The State University of New Jersey	Camden
M1370	Rutgers, The State University of New Jersey	New Brunswick
M1370	Rutgers, The State University of New Jersey	Newark
M1465	UMDNJ—New Jersey Dental School	Newark
M1466	UMDNJ—New Jersey Medical School, including	Newark
M1466	School of Nursing and University Hospital	
M1464	UMDNJ—New Jersey School of Osteopathic Medicine	Camden
M1467	UMDNJ—Robert Wood Johnson Medical School (formerly	Piscataway
M1467	Rutgers Medical School), including RWJ	
M1467	University Hospital (formerly Middlesex Hospital)	New Brunswick
	New Mexico	
M1479	Lovelace Institutes, including Clinic Foundation and	Albuquerque
M1479	Institute for Basic and Applied Medical Research	
M1479	Institute for Health and Population Research	
M1479	Lovelace Biomedical, and Environmental Research Institute	
M1479	Lovelace Scientific Resources	

Assurance Number	State/Institution	City
M1330-XM	New Mexico, University of	Albuquerque
M1450	New Mexico, University of, Medical Center, including	Albuquerque
M1450	Cancer Center	
M1450	Center for Non-Invasive Diagnosis	
M1450	Colleges of Nursing and Pharmacy	
M1450	University of New Mexico Health Programs	
M1450	University of New Mexico Hospital	
M1450	Veterans Affairs, Dept. of, Regional Medical Center	Albuquerque
	New York	
M1487	Addiction Research & Treatment Corporation	Brooklyn
M1187	Agricultural and Technical College, SUNY	Farmingdale
M1121	Albany Medical College	Albany
M1519	Albany/Research Institute and VA Medical Center	Albany
M1063	Albert Einstein College of Medicine of Yeshiva Univ.,	Bronx
M1063	including Ferhauf Graduate School of Psychology and	
M1063	Wurzheiler School of Social Work	
M1193	American Health Foundation	New York
M1313-XB	Associated Universities, Inc., including	Upton
M1313-XB	Brookhaven National Laboratory, and	
M1313-XB	Clinical Research Center	
M1381	Beth Israel Medical Center, also	New York
M1381	Hospital for Joint Diseases	
M1381	New York Eye & Ear Infirmary, and	
M1381	Schnurmacher Nursing Home	
M1518	Bronx Lebanon Hospital Center	Bronx
M1313-XB	Brookhaven National Laboratory (Associated Universities)	Upton
M1374-XM	Canisius College	Buffalo
M1500	Central New York Research Corp./VA Medical Center	Syracuse
M1314	Children's Hospital of Buffalo	Buffalo
M1356	Columbia—Presbyterian Hospital of NYC, including Health	New York
M1356	Sciences Division of Columbia University and Presbyterian	
M1356	Hospital (including Allen Pavilion, Atchley Pavilion,	
M1356	Babies Hospital, Eastside Practice Site, Harkness Eye	
M1356	Institute, Harkness Pavilion, Milstein Hospital Building,	
M1356	Neurological Institute, New York Orthopaedic Hospital,	
M1356	Radiation Therapy Center, Sloane Hospital for Women,	
M1356	Squire Urological Clinic, and Vanderbilt Clinic	
M1309-XM	Columbia University, except Health Science Division	New York
M1356	Columbia University Health Science Division (including	New York
M1356	College of Physicians & Surgeons, Programs in Occupational	
M1356	and Physical Therapy, Schools of Dental and Oral Surgery,	
M1356	Nursing and Public Health) and Presbyterian Hospital in NYC	
M1393-XM	Columbia University, Teacher's College	New York
M1269	Cornell University (except University Medical Center)	Ithaca

Assurance Number	State/Institution	City
M1185	Cornell University Medical Center: See New York Hospital.	New York
M1178-XB	Eastman Dental Center	Rochester
M1142-XM	Empire State College SUNY	Saratoga Springs
M1463	Fordham University	Bronx
M1058-XB	Genesee Hospital	Rochester
M1037	Health Research, Inc., Roswell Park Division	Buffalo
M1241-XB	Helen Hayes Hospital/New York State Department of Health	West Haverstraw
M1381	Hospital for Joint Diseases: See Beth Israel Medical Center.	New York
M1109	Hospital for Special Surgery	New York
M1351	Jewish Board of Family and Children's Services, Inc.	New York
M1007	Kingsbrook Jewish Medical Center, including	Brooklyn
M1007	David Minkin Rehabilitation Institute and	
M1007	Rutland Nursing Home	
M1097	Long Island Jewish-Hillside Medical Center, including	New Hyde Park
M1097	Schneider Children's Hospital and Hillside Hospital-Glen Oaks	
M1333-XB	Maimonides Medical Center	Brooklyn
M1151	Mary Imogene Bassett Hospital	Cooperstown
M1210	Memorial Sloan Kettering Cancer Center	New York
M1062	Montefiore Hospital and Medical Center, including	Bronx
M1062	Henry and Lucy Moses Hospital Division, and	
M1062	Jack D. Weiler Hospital of Albert Einstein College of Medicine	
M1155	Mount Sinai Medical Center, School of Medicine and	New York
M1155	Mount Sinai Hospital, of CUNY	
M1501	Narrows Institute for Biomedicine & Research/	Brooklyn
M1501	VA Medical Center	
M1055	Nassau County Medical Center, including	East Meadow
M1055	Meadowbrook Medical Education and Research Foundation, Inc.	
M1492	National Development & Research Institutes, Inc.	Albany, NYC
M1492	(was Narcotic & Drug Research, Inc.), including	
M1492	Social Sciences Innovations	
M1445-XM	New School for Social Research	New York
M1052	New York Blood Center, Inc., including	New York
M1052	Blood Services: Hudson Valley, Long Island,	
M1052	New Jersey, and New York	
M1052	Lindsley F. Kimball Research Institute	
M1052	Melville Biologics	
M1111-XM	New York, City University of, Bernard Baruch College	New York
M1111-XM	New York, City University of, Bronx Community College	Bronx
M1111-XM	New York, City University of, Brooklyn College	Brooklyn
M1111-XM	New York, City University of, City College	New York
M1111-XM	New York, City University of, College of Staten Island	Staten Island
M1111-XM	New York, City University of, Graduate School	New York
M1111-XM	and University Center	
M1111-XM	New York, City University of, Hostos Community College	Bronx
M1111-XM	New York, City University of, Hunter College	New York
M1111-XM	New York, City University of, John Jay College	New York

Assurance Number	State/Institution	City
M1111-XM	of Criminal Justice	
M1111-XM	New York, City University of, Kingsboro Community College	Brooklyn
M1111-XM	New York, City University of, LaGuardia Community College	Long Island City
M1111-XM	New York, City University of, Lehman College	Bronx
M1111-XM	New York, City University of, Medgar Evers College	Brooklyn
M1111-XM	New York, City University of, New York City Technical College	Brooklyn
M1111-XM	New York, City University of, Queens College	Flushing
M1111-XM	New York, City University of, Queensborough	New York
M1111-XM	Community College	
M1111-XM	New York, City University of, Research Foundation	New York
M1111-XM	New York, City University of, York College	Jamaica
M1185	New York Hospital—Cornell Medical Center, Inc.	New York
M1185	Cornell University Graduate School of Medical Sciences	
M1185	Cornell University Medical College	
M1185	New York Hospital	
M1185	Rogosin Institute, Inc.	
M1327	New York Medical College (Graduate School of Medical	Valhalla
M1327	Sciences, Graduate School of Health Sciences & Medical School)	
M1241	New York State Department of Health, Health Research, Inc.	Albany
M1241	(Albany Division)/Helen Hayes Hospital	
M1376	New York State Department of Mental Hygiene, including	Albany
M1376	component agencies and Research Foundation for Mental	
M1376	Hygiene, Inc. (multiple sites)	
M1449	New York, State University of, at Albany	Albany
M1209	New York, State University of, at Binghamton	Binghamton
M1270	New York, State University of, at Buffalo	Buffalo
M1036	New York, State University of, at Stony Brook	Stony Brook
M1064-XM	New York, State University of, College at Brockport,	Brockport
M1064-XM	including Educational Opportunity, and Rochester Center	
M1420-XM	New York, State University of, College at Buffalo	Buffalo
M1010-XM	New York, State University of, College at Cortland	Cortland
M1326-XM	New York, State University of, College at Geneseo	Geneseo
M1242	New York, State University of, College of Optometry	New York
M1187-XM	New York, State University of, College of Technology	Farmingdale
M1187-XM	at Farmingdale	
M1142-XM	New York, State University of, Empire State College	Saratoga Springs
M1073	New York, State University of, Health Science	Brooklyn
M1073	Center at Brooklyn (formerly Downstate Medical Center)	
M1073	& State University Hospital, including University Hospital	
M1303	New York, State University of, Health Science Center	Syracuse
M1303	(formerly Upstate Medical Center) including Univ. Hospital	
M1250	New York University, except the Medical Center	New York
M1177	New York University Medical Center, including School of	New York
M1177	Medicine, Rusk Institute of Rehabilitative Medicine,	
M1177	Schwartz Health Care Center, Skirball Institute of	

Assurance Number	State/Institution	City
M1177	Biomolecular Medicine, and Tisch Hospital	
M1302	North Shore University Hospital	Manhasset
M1356	Presbyterian Hospital of NYC: See Columbia-	New York
M1356	Presbyterian Hospital.	
M1300	Rensselaer Polytechnic Institute	Troy
M1376	Research Foundation for Mental Hygiene, Inc. of	Albany
M1376	New York State (multiple sites)	
M1111-XM	Research Foundation of the City University of New York	New York
M1357	Rochester, University of, including College of	Rochester
M1357	Arts & Sciences, College of Engineering & Applied Science,	
M1357	Eastman School of Music, Graduate School of Education &	
M1357	Human Development, School of Medicine & Dentistry,	
M1357	School of Nursing, Strong Memorial Hospital, Wm. Simon	
M1357	Graduate School of Business Administration	
M1185	Rogosin Institute Inc. (New York Hospital—Cornell	New York
M1185	Medical Center)	
M1297	Rockefeller University, including University Hospital	New York
M1037	Roswell Park Cancer Institute and Health	Buffalo
M1037	Research, Inc.—Roswell Park Division	
M1210	Sloan-Kettering Institute for Cancer Research	New York
M1210	(Memorial Sloan-Kettering Cancer Center)	
M1083	St. Johns University	Jamaica
M1253	St. Luke's Roosevelt Institute for Health Science	New York
M1253	(including St. Luke's—Roosevelt Hospital Center)	
M1277-XB	St. Mary's Hospital	Rochester
M1227	St. Vincent's Hospital & Medical Center of New York,	New York
M1227	including St. Vincent's School of Nursing	
M1357	Strong Memorial Hospital: See Rochester, University of.	Rochester
M1054-XM	Syracuse University	Syracuse
M1444	Veterans Affairs, Dept. of, Hospital	Northport
M1501	Veterans Affairs, Dept. of, Medical Center/The Narrows	Brooklyn
M1501	Institute for Biomedicine and Research	
M1500	Veterans Affairs, Dept. of, Medical Center/Central	Syracuse
M1500	New York Research Corp.	
M1519	Veterans Affairs, Dept. of, Samuel S. Stratton	Albany
M1519	Medical Center and Albany Research Institute	
M1063	Yeshiva University, Albert Einstein College of Medicine	Bronx
	North Carolina	
M1161	Bowman Gray School of Medicine (Wake Forest University),	Winston-Salem
M1161	including North Carolina Baptist Hospitals	
M1106	Duke University Medical Center	Durham
M1414-XM	Duke University, except the Medical Center	Durham
M1141	National Center for Health Statistics, CDC	Res. Triangle Park
M1141	(also Maryland)	

Assurance Number	State/Institution	City
M1389	North Carolina A&T State University	Greensboro
M1161	North Carolina Baptist Hospital (Bowman	Winston-Salem
M1161	Gray School of Medicine)	
M1263-XM	North Carolina State University at Raleigh	Raleigh
M1390	North Carolina, University of, at Chapel Hill	Chapel Hill
M1496	Research Triangle Institute (RTI)	Res. Triangle Park
M1161-XB	Wake Forest University, Bowman Gray School of Medicine	Winston-Salem
M1335	Wake Forest University, except School of Medicine	Winston-Salem
M1391	Western Carolina Center and Foundation	Morganton
	Ohio	
M1159	Akron General Medical Center	Akron
M1077	Akron, University of	Akron
M1221	Battelle Memorial Institute, Columbus operations	Columbus
M1186-XM	Bowling Green State University	Bowling Green
M1521	Case Western Reserve University, including	Cleveland
M1521	MetroHealth Medical Center, University Hospitals,	
M1521	and VA Medical Center	
M1170	Children's Hospital Medical Center	Cincinnati
M1424	Children's Hospital Research Foundation, including	Columbus
M1424	Children's Hospital and Children's Guidance Center	
M1138	Cincinnati, University of, including Medical Center and	Cincinnati
M1138	Barret Cancer Center	
M1388	Cleveland Clinic Foundation and	Cleveland
M1388-XB	Cleveland Clinic Education Foundation, including Research Inst.	
M1021	Cox Heart Institute	Dayton
M1021	Fels Research Institute	Yellow Springs
M1107-XB	Jewish Hospital of Cincinnati, including	Cincinnati
M1107	Children's Psychiatric Center and Institute for	
M1107	Advanced Nursing Clinical Education	
M1312	Kaiser Foundation Hospitals (Ohio Region)	Cleveland
M1312	Parma Medical Center—Parma	
M1282	Kent State University and Foundation	Kent
M1166-XB	Marymount Hospital	Garfield Heights
M1358	Medical College of Ohio at Toledo, including	Toledo
M1358	Center for Environmental Medicine	
M1358	Coughlin Rehabilitation Hospital	
M1358	Educare Center	
M1358	Family Practice Center	
M1358	Foundation Park Care Center	
M1358	Geriatric Center	
M1358	Glendale Medical Center	
M1358	Image Analysis Research Center	
M1358	Kobacker Center	
M1358	Medical College Hospital	

Assurance Number	State/Institution	City
M1358	Morse Center	
M1358	Rehab Works	
M1358	Reuben Center for Women and Children	
M1358	Ruppert Health Center	
M1521	MetroHealth Medical Center/Case Western Reserve University ...	Cleveland
M1521	and VA Medical Center	
M1104	Mount Sinai Medical Center	Cleveland
M1220	National Institute for Occupational Safety & Health	Cincinnati
M1238	Ohio State University, Research Foundation & Univ. Hospital ...	Columbus
M1138	Shriner's Burns Institute/University of Cincinnati	Cincinnati
M1521	University Hospitals (Case Western Reserve University)	Cleveland
M1138	Veterans Affairs, Dept. of, Medical Center/Univ. of Cincinnati ...	Cincinnati
M1521	Veterans Affairs, Dept. of, Medical Center/Case	Cleveland
M1521	Western Reserve University and MetroHealth Medical Center	
M1021	Wright State University, including	Dayton
M1021	Cox Institute	
M1021	Duke E. Ellis Institute	
M1021	Yellow Springs Family Health Center	
	Oklahoma	
M1092-XB	Oklahoma Medical Research Foundation, Inc.	Oklahoma City
M1146	Oklahoma, University of	Norman
M1448	Oklahoma, University of, Health Sciences Center	Oklahoma City
	Oregon	
M1517	CareMark/Managed Healthcare Northwest PPO	Portland
M1517	of Legacy Health System	
M1517	Emanuel Hospital & Health Center of Legacy Health System	Portland
M1517	Good Samaritan Hospital & Medical Center	Portland
M1517	of Legacy Health System	
M1517	Holladay Park Medical Center of Legacy Health System	Portland
M1312	Kaiser Foundation Hospitals (Northwest Region)	Portland
M1312	Beth Kaiser Medical Center Sunnyside Medical Center	
M1517	Legacy Health System (See 5 named Hospitals.)	Portland
M1517	Legacy Visiting Nurse Association of Legacy Health System	Portland
M1323	Medical Research Foundation of Oregon and	Portland
M1323	Oregon Regional Primate Research Center	
M1517	Meridian Park Hospital of Legacy Health System	Portland
M1517	Mt. Hood Medical Center of Legacy Health System	Portland
M1211-XM	Northwest Regional Educational Laboratory	Portland
M1359	Oregon Health Sciences University, including	Portland
M1359	Schools of Medicine, Dentistry, and Nursing	
M1215-XM	Oregon Research Institute	Eugene
M1447	Oregon Social Learning Center (formerly	Eugene
M1447	Evaluation Research Group)	

Assurance Number	State/Institution	City
M1099	Oregon State University	Corvallis
M1143	Oregon, University of	Eugene
	Pennsylvania	
M1212	Albert Einstein Medical Center, Northern Division/	Philadelphia
M1212	Belmont Center for Comprehensive Treatment	
M1050	Allegheny-Singer Research Corporation	Pittsburgh
M1050	& Allegheny General Hospital	
M1050	Allegheny General Hospital, including	Pittsburgh
M1050	Allegheny Neuropsychiatric Institute	
M1050	Allegheny Singer Research Institute (Continuing	
M1050	Care Center/AGH and North Hills Recovery Center in Wexford)	
M1212	Belmont Center for Comprehensive Treatment	Philadelphia
M1212	(was Philadelphia Psychiatric Center)/Albert Einstein	
M1212	Medical Center	
M1462	Carnegie-Mellon University	Pittsburgh
M1257	Children's Hospital of Philadelphia	Philadelphia
M1257	(Joseph Stokes, Jr. Research Institute of)	
M1230	Children's Hospital of Pittsburgh	Pittsburgh
M1030	Fox Chase Cancer Center (Divisions of	Philadelphia
M1030	Jeanes Hospital, Medical Science, Basic Science,	
M1030	and Population Science)	
M1156-XB	Geisinger Medical Center, Institute for	Danville
M1156-XB	Medical Education and Research	
M1016	Graduate Hospital	Philadelphia
M1116	Hahnemann University: School of Medicine, Graduate School,	Philadelphia
M1116	University Hospital, School of Health Sciences & Humanities	
M1030	Jeanes Hospital/Fox Chase Cancer Center	Philadelphia
M1226-XB	Lankenau Medical Research Center and Lankenau Hospital	Philadelphia
M1399	Magee-Womens Hospital	Pittsburgh
M1139	Medical College of Pennsylvania	Philadelphia
M1027	Milton S. Hershey Medical Center (Penn. State University)	Hershey
M1025	Monell Chemical Senses Center	Philadelphia
M1225	Norristown State Hospital	Norristown
M1200-XB	Pennsylvania College of Podiatric Medicine	Philadelphia
M1113	Pennsylvania Hospital/Institute of Pennsylvania Hospital	Philadelphia
M1145	Pennsylvania State University (20 campuses)	University Park
M1027	Pennsylvania State University Milton S. Hershey Med. Center	Hershey
M1027	(College of Medicine, University Hospital, Children's Hosp.)	
M1025	Pennsylvania, University of	Philadelphia
M1029	Philadelphia Department of Public Health	Philadelphia
M1322	Philadelphia Geriatric Center, including	Philadelphia
M1322	Edward and Esther Polisher Research Institute	
M1212	Philadelphia Psychiatric Center: See Belmont Center	Philadelphia
M1259	Pittsburgh, University of, including	Pittsburgh

Assurance Number	State/Institution	City
M1259	Pittsburgh Cancer Center	
M1103	Presbyterian Medical Center, including	Philadelphia
M1103	Philadelphia Heart Institute & Scheie Eye Institute	
M1442	St. Christopher's Hospital for Children/Temple University	Philadelphia
M1001	St. Joseph's Hospital	Lancaster
M1422	Temple University (except Health Sciences Center)	Philadelphia
M1442	Temple University Health Sciences Center, including	Philadelphia
M1442	College of Allied Health Professions, School of Dentistry,	
M1442	School of Medicine, School of Pharmacy, St. Christopher's	
M1442	Hospital for Children and Temple University Hospital	
M1115	Thomas Jefferson University, including	Philadelphia
M1115	Children's Rehabilitation Hospital	
M1115	College of Allied Health Sciences	
M1115	College of Graduate Studies	
M1115	Jefferson Medical College	
M1115	Thomas Jefferson University Hospitals—	
M1115	Ford Road Campus and Philadelphia	
M1528	Veterans Affairs, Department of Medical Center	Philadelphia
M1231-XB	Wills Eye Hospital and Research Institute	Philadelphia
M1347-XB	Wistar Institute	Philadelphia
	Rhode Island	
M1411	Brown University	Providence
M1126	Memorial Hospital	Pawtucket
M1369	Miriam Hospital	Providence
M1307	Rhode Island Hospital	Providence
M1481	Rhode Island, State of, Providence	Providence
M1481	Plantations (Rhode Island Dept. of Health)	
M1457	Rhode Island, University of	Kingston
M1041	Roger Williams Hospital	Providence
	South Carolina	
M1368	Clemson University	Clemson
M1012	Medical University of South Carolina/Ralph H.	Charleston
M1012	Johnson VA Center, including Charleston Memorial Hospital	
M1075-XB	South Carolina Dept. of Health and Environmental Control	Columbia
M1281	South Carolina Dept. of Mental Health, including	Columbia
M1281	C.M. Tucker Human Resources Center	Columbia
M1281	Crafts-Farrow State Hospital	Columbia
M1281	Dowdy-Gardner Nursing Care Center	Columbia
M1281	Dowdy-Gardner Nursing Care Center	Rockhill
M1281	Earl Morris Alcohol & Drug Addiction Center	Columbia
M1281	G. Werber Bryan Psychiatric Hospital	Columbia
M1281	J.F. Byrnes Medical Center	Columbia
M1281	Patrick B. Harris Psychiatric Hospital	Anderson

Assurance Number	State/Institution	City
M1281	Richard Campbell Nursing Home	Anderson
M1281	South Carolina State Hospital	Columbia
M1281	William S. Hall Psychiatric Hospital	Columbia
M1180	South Carolina, University of, including Medical School	Columbia
M1012	Veterans Affairs, Dept. of, Ralph H. Johnson Center/	Charleston
M1012	Medical University of South Carolina	
M1495	Veterans Affairs, Dept. of, William J.B. Dorn Hospital	Columbia
	South Dakota	
M1206	South Dakota, University of	Vermillion
M1216	South Dakota, University of, Medical School & Univ. Physicians	Sioux Falls
M1206	South Dakota, University of, Medical School	Yankton
	Tennessee	
M1194	East Tennessee State University &	Johnson City
M1194	James Quillen College of Medicine/VA Medical Center	
M1384	Meharry Medical College	Nashville
M1485	Memphis, University of (was Memphis State College)	Memphis
M1394	Oak Ridge Associated Universities	Oak Ridge
M1394	Oak Ridge National Laboratory	Oak Ridge
M1013-XB	St. Jude Children's Research Hospital	Memphis
M1249-XM	Tennessee State University	Nashville
M1081	Tennessee, University of—Knoxville	Knoxville
M1056	Tennessee, University of, at Memphis, including	Memphis
M1056	Medical Center at Knoxville	
M1363	Vanderbilt University, including George Peabody College for	Nashville
M1363	Teachers and VA Medical Center	
M1194	Veterans Affairs, Dept. of, Medical Center/East Tennessee	Johnson City
M1194	State University	
M1363	Veterans Affairs, Dept. of, Medical Center/	Nashville
M1363	Vanderbilt University	
	Texas	
M1453	Baylor, College of Dentistry	Dallas
M1060	Baylor, College of Medicine	Houston
M1067	Houston, University of (Central Campus only)	Houston
M1105	Humana Hospital–Metropolitan	San Antonio
M1098	M.D. Anderson Hospital: See Texas, Univ. of, Cancer Center.	Houston
M1136	North Texas, University of/Texas College of	Fort Worth
M1136	Osteopathic Medicine	
M1471	Rice University	Houston
M1308	Texas A&M University, including	College Station
M1308	Institute of Biosciences & Technology, Houston	
M1308	Santa Fe Research Center—Temple	

Assurance Number	State/Institution	City
M1308	Texas Agricultural Experimental Station	
M1308	Texas Agricultural Extension Service	
M1308	Texas Engineering Experiment Station	
M1308	Texas Engineering Extension Service	
M1308	Texas Transportation Institute	
M1308	Texas A&M University	Galveston
M1136	Texas College of Osteopathic Medicine/University of N. Texas	Fort Worth
M1213	Texas Tech University	Lubbock
M1078-XB	Texas Tech University Health Sciences Center, including	Lubbock
M1078-XB	Amarillo, El Paso, and Odessa campuses	
M1110	Texas, University of, at Austin	Austin
M1059-XM	Texas, University of, at Dallas	Richardson
M1251-XM	Texas, University of, at El Paso	El Paso
M1098	Texas, University of, Cancer Center (and its	Houston
M1098	M.D. Anderson Hospital and Tumor Institute)	
M1486	Texas, University of, Health Center at Tyler	Tyler
M1246	Texas, University of, Health Science Center	Houston
M1246	at Houston, including Harris County Psychiatric Center	
M1403	Texas, University of, Health Science Center	San Antonio
M1403	at San Antonio/Audie L. Murphy VA Hospital/Cancer	
M1403	Treatment & Research Center Research Foundation, including	
M1403	Medical School, Dental School, and Graduate School of	
M1403	Biomedical Sciences; School of Nursing; School of Allied	
M1403	Health Sciences; and Graduate School of Pharmacy	
M1172	Texas, University of, Medical Branch at Galveston	Galveston
M1304	Texas, University of, Southwestern Medical Center	Dallas
M1304	at Dallas, including SW Medical School, SW Graduate	
M1304	School of Biomedical Sciences, and SW School of	
M1304	Allied Health Sciences	
M1514	Veterans Affairs, Dept. of, Medical Center	Dallas
M1403	Veterans Affairs, Dept. of, Hospital (Audie L. Murphy	San Antonio
M1403	Memorial)/Texas, University of, including CTRC	
M1403	Research Foundation, Cancer Center and Research Center	
M1403	Health Science Center	
	Utah	
M1089	LDS Hospital	Salt Lake City
M1152	Utah State University	Logan
M1082	Utah, University of, including the Research Institute	Salt Lake City
	Vermont	
M1375	Vermont, University of, and State	Burlington
M1375	Agricultural College	
M1375	Medical Center Hospital of Vermont	
M1375	University Health Center	

Assurance Number	State/Institution	City
	Virginia	
M1355	Eastern Virginia Medical School of Medical College of	Norfolk
M1355	Hampton Roads	
M1195-XM	Human Resources Research Organization, including	Alexandria
M1195-XM	Human Resources Research Organization International, Inc.	
M1525	Salem Research Institute Inc./VA Medical Center	Salem
M1315	Virginia Commonwealth University (All Schools	Richmond
M1315	and Divisions)	
M1506	Virginia Polytechnic Institute & State University	Blacksburg
M1343	Virginia, University of	Charlottesville
M1525	Veterans Affairs, Dept. of, Medical Center/Salem	Salem
M1525	Research Institute, Inc.	
	Washington	
M1214	Children's Hospital and Medical Center, and Odessa	Seattle
M1214	Brown Children's Clinic	
M1008	Fred Hutchinson Cancer Research Center	Seattle
M1507	Group Health Cooperative, Puget Sound	Seattle
M1008	Swedish Medical Center/Swedish Medical Center—Ballard	Seattle
M1040	Virginia Mason Research Center, including	Seattle
M1040	Virginia Mason Clinic and Virginia Mason Hospital	
M1076	Washington State Dept. of Health	Olympia
M1076	Washington State Dept. of Social & Health Services	Olympia
M1076	(All Components)	
M1344	Washington State University, including	Pullman
M1344	branch campuses: Pullman, Spokane, Vancouver, and	
M1344	Tri-Cities at Richland	
M1183	Washington, University of, including	Seattle
M1183	University Medical Center and Harborview Medical Center	
M1183	Burke Memorial Washington State Museum	
	West Virginia	
M1044	Marshall University	Huntington
M1220	National Institute for Occupational Safety & Health	Morgantown
M1491	Veterans Affairs, Dept. of, Medical Center	Huntington
M1256	West Virginia University and West Virginia Research Fdn.,	Morgantown
M1256	including Charleston Area Medical Division and	
M1256	University Hospital	
	Wisconsin	
M1480-XB	Blood Center of Southeastern Wisconsin, Inc.	Milwaukee
M1392-XM	Marquette University	Milwaukee
M1512	Marshfield Medical Research & Education Foundation	Marshfield
M1512	(22 locations)	

Assurance Number	State/Institution	City
M1061	Medical College of Wisconsin, including	Milwaukee
M1061	Children's Hospital of Wisconsin	
M1061	Clinical Research Center	
M1061	Curative Rehabilitation Center	
M1061	Froedert Memorial Lutheran Hospital	
M1061	John L. Doyne Hospital	
M1061	Milwaukee County Medical Health Complex	
M1061	Veterans Affairs Medical Center	
M1423	Mendota Mental Health Institute Program for	Madison
M1423	Assertive Community Treatment (PACT)	
M1120	Sinai Samaritan Medical Center	Milwaukee
M1085	Southern Wisconsin Center for the Developmentally Disabled	Union Grove
M1061	Veterans Affairs, Dept. of, Medical Center	Milwaukee
M1285	Wisconsin, University of, Madison Campus	Madison
M1198	Wisconsin, University of	Milwaukee
M1334	Wisconsin, University of, Parkside	Kenosha
	Canada	
M1458	McGill University	Montreal
	Puerto Rico	
M1035-XM	Catholic University of Puerto Rico	Ponce
M1291-XB	Puerto Rico, University of, Medical Sciences Campus	San Juan
M1291-XB	and University Hospital	

Restriction Codes:

XM—No Medical or IND Studies
XB—No Behavioral Studies

F. The National Bioethics Advisory Commission

A Brief History

During the 1970s and 1980s, several distinguished commissions in the United States studied various aspects of medical bioethics including the protection of human subjects of biomedical and behavioral research and ethical problems in medicine and research. Several of these commissions have influenced medical and research practices over the years. In the intervening years, the pace of medical and scientific progress has quickened. Advances in human genome research, linked to the joint DOE-NIH Human Genome Project, have heightened concerns about the use of human subjects in medical research as well as long-standing concerns about human embryo and fetal research that have accompanied advances in prenatal and neonatal medicine. Many, both in Congress and outside, have suggested that a new commission focusing on these ethically troublesome areas is timely. Additionally, the advent of early and experimental forms of somatic gene therapy for enzyme disorders has highlighted the proximity of this novel form of medical intervention to the plethora of ethical issues associated with it.

In response to these urgings, and following a report by the Congressional Office of Technology Assessment (Biomedical Ethics in U.S. Public Policy—Background Paper OTA-BP-BBS-105, June 1993), the White House Office of Science and Technology Policy proposed the establishment of a National Bioethics Advisory Commission (NBAC). This commission, with 15 members encompassing a wide range of relevant disciplines and appointed by the President, would be linked to the National Science and Technology Council, and study issues associated with the management and use of genetic information, including but not limited to human gene patenting and the protection of the rights and welfare of research subjects. The intent of NBAC is to address those issues that are sufficiently urgent, related to Administration goals for Federal investment in science and technology, not being dealt with by other appropriate bodies, and of interest or relevance to more than one agency or department. The reports, advice, and recommendations of the NBAC will be made public. In this way, it is hoped that careful and informed consideration and reflection can be given to some of the serious issues in bioethics so that collective wisdom can inform public policy making at a sufficiently early stage to be influential. (The NBAC is expected to become established late in 1995.)

Following is the draft Executive Order dated August 21, 1995, for the establishment of the National Bioethics Advisory Commission.

National Bioethics Advisory Commission—Draft Executive Order

8/21/95
DRAFT
EXECUTIVE ORDER

NATIONAL BIOETHICS ADVISORY COMMISSION

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. Establishment. (a) There shall be established a National Bioethics Advisory Commission (NBAC). NBAC shall be composed of not more than 15 members to be appointed by the President. NBAC shall comply with the Federal Advisory Committee Act, as amended, 5 U.S.C. App. 2.

(b) The President shall designate a Chairperson from among the members of NBAC.

Section 2. Functions. NBAC will provide advice and make recommendations to the National Science and Technology Council and other appropriate entities. NBAC's purview includes the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior, and applications, including the clinical applications, of that research. NBAC shall identify broad, overarching principles to govern the ethical conduct of research, citing individual projects only as illustrations for such principles. NBAC shall not be responsible for the review and approval of individual projects.

As a first priority, NBAC will direct its attention to consideration of:

A. Protection of the rights and welfare of research subjects; and

B. Issues in the management and use of genetic information, including but not limited to, human gene patenting.

In addition to responding to requests for advice and recommendations from the National Science and Technology Council, NBAC shall have the authority to identify bioethical issues, on its own behalf, for deliberation. NBAC will also accept suggestions of issues for consideration from Congress and the public. NBAC shall consider four criteria in establishing priority for its activities:

A. The public health or public policy urgency of the bioethical issue.
B. The relation of the bioethical issue to the goals for Federal investment in science and technology.
C. The absence of another body able to fruitfully deliberate on the bioethical issue.
D. The extent of interest in the issue across the government. (NBAC ordinarily will not deliberate on a bioethical issue of interest to just one department or agency.)

Continued—

National Bioethics Advisory Commission—Draft Executive Order *(continued)*

Section 3. Administration. (a) The heads of executive departments and agencies shall, to the extent permitted by law, provide NBAC with such information as it may require for purposes of carrying out its functions.

(b) The Commission may conduct inquiries, hold hearings and establish subcommittees, as necessary. The Assistant to the President for Science and Technology shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration of the subcommittee, and estimated frequency of meetings.

The Commission is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on the Commission, the Commission is also authorized to contract for the services of non-governmental consultants who may conduct analyses, prepare reports and background papers or prepare other materials for consideration by the Commission, as appropriate.

(c) Members of NBAC shall be compensated in accordance with Federal law. Members of NBAC may be allowed travel expenses, including per diem in lieu of subsistence, to the extent permitted by law for persons serving intermittently in the government service (5 U.S.C. 5701–5707).

(d) To the extent permitted by law, and subject to the availability of appropriations, the Department of Health and Human Services (DHHS) shall provide NBAC with such funds as may be necessary for the performance of its functions. The Office for Protection from Research Risks, DHHS, will provide management and support services to NBAC.

Section 4. General Provisions. (a) Notwithstanding the provisions of any other Executive Order, the functions of the President under the Federal Advisory Committee Act that are applicable to NBAC, except that of reporting annually to Congress, shall be performed by OPRR, in accordance with the guidelines and procedures established by the Administrator of General Services.

(b) NBAC shall terminate two years from the date of this order unless extended prior to that date.

(c) This order is intended only to improve the internal management of the Executive Branch and it is not intended to create any right, benefit, trust, or responsibility, substantive or procedural, enforceable at law or equity by a party against the United States, its agencies, its officers, or any person.

National Bioethics Advisory Commission—Revised Charter

2-23-95
DRAFT

NATIONAL BIOETHICS ADVISORY COMMISSION REVISED CHARTER

Purpose

The National Bioethics Advisory Commission will provide advice and make recommendations to the National Science and Technology Council, other appropriate entities and the public, on bioethical issues arising from research on human biology and behavior, and the applications, including the clinical applications, of that research.

Authority

42 U.S.C. 6617(a)(2). This Commission is governed by the provisions of the Federal Advisory Committee Act (FACA), Public Law 92-463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation of advisory committees, and implementing regulations (41 C.F.R. § 101–6.10).

Functions

The National Bioethics Advisory Commission shall advise, consult with, and make recommendations to the National Science and Technology Council, Federal agencies, and other appropriate entities, and also make their advice and recommendations available to the public. The Commission's purview includes the appropriateness of departmental, agency, or other governmental programs, policies, assignments, missions, guidelines, and regulations as they relate to bioethical issues arising from research on human biology and behavior, and applications, including the clinical applications, of that research. The Commission shall identify broad, overarching principles to govern the ethical conduct of research, citing individual projects only as illustrations for such principles. The Commission shall not be responsible for the review and approval of individual projects.

As a first priority, the Commission will direct its attention to consideration of:

A. Issues in the management and use of genetic information including but not limited to human gene patenting; and
B. Protection of the rights and welfare of research subjects.

In addition to responding to requests for advice and recommendations from the National Science and Technology Council, the Commission shall have the authority to identify bioethical issues, on its own behalf, for deliberation. The Commission will also accept suggestions of issues for consideration from Congress and the public. The Commission shall consider four criteria in establishing priority for its activities:

A. The public health or public policy urgency of the bioethical issue.
B. The relation of the bioethical issue to the goals for Federal investment in science and technology.
C. The absence of another body able to fruitfully deliberate on the bioethical issue.
D. The extent of interest in the issue across the government. (The Commission ordinarily will not deliberate on a bioethical issue of interest to just one department or agency.)

Continued—

National Bioethics Advisory Commission—Revised Charter *(continued)*

Structure

The National Bioethics Advisory Commission shall consist of not more than 15 members including the Chairperson. Appointments shall be made by the President, who shall select from knowledgeable non-Government experts and community representatives with special qualifications and competence to deal effectively with bioethical issues of concern to the participating departments and agencies. At least one member shall be selected from each of the following categories of primary expertise: (i) philosophy/ theology; (ii) social/behavioral science; (iii) law; (iv) medicine/allied health professions; and (v) biological research. At least three members shall be selected from the general public, bringing to the Commission expertise other than that listed. The membership shall be approximately evenly balanced between scientists and non-scientists. Close attention will be given to equitable geographic distribution and to ethnic and gender representation.

Members shall be appointed for overlapping four-year terms. Initially, members will be appointed for two-, three- or four-year terms. Terms of more than two years are contingent upon renewal of the National Bioethics Advisory Commission by appropriate action prior to its termination. The Chairperson shall be appointed by the President. The term of office for the Chairperson shall be two years, renewable by appropriate action of the President.

If a vacancy occurs on the Commission, the President shall make an appointment to fulfill the term. Any member appointed to fill a vacancy occurring prior to expiration of the term for which his or her predecessor was appointed shall serve for the remainder of such term. Members may serve after the expiration of their terms until their successors have taken office.

The Commission may conduct inquiries, hold hearings and establish subcommittees, as necessary.

The Commission is authorized to conduct analyses and develop reports or other materials. In order to augment the expertise present on the Commission, the Commission is also authorized to contract for the services of non-governmental consultants who may conduct analyses, prepare reports and background papers or prepare other materials for consideration by the Commission, as appropriate.

In order to avoid duplication of effort, the Commission is encouraged to review the deliberations of other entities. The Commission may incorporate or otherwise use the results of the deliberations of other entities as it deems appropriate.

The Assistant to the President for Science and Technology shall be notified upon establishment of each subcommittee, and shall be provided information on the name, membership (including chair), function, estimated duration of the subcommittee, and estimated frequency of meetings.

Management and support services shall be provided by the Office for Protection from Research Risks, Department of Health and Human Services. Additional resources including, but not limited to personnel, office support and printing will be provided by other NSTC member agencies.

Continued—

National Bioethics Advisory Commission—Revised Charter *(continued)*

Meetings

Meetings of the Commission shall be held up to 10 times a year at the call of the Chairperson. Meetings of the subcommittee(s) shall be convened as necessary. A Federal Government official shall be present at all meetings.

Meetings shall be open to the public except as determined otherwise by the Assistant to the President for Science and Technology. Advance notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of proceedings kept, as required by applicable laws and Federal regulations.

Compensation

Members may be compensated at a rate not to exceed the maximum pay authorized by 5 U.S.C. 3109, plus per diem and travel expenses as in accordance with standard government travel regulations.

Annual Cost Estimate

The estimated annual cost for operating the National Bioethics Advisory Commission, including compensation and travel expenses for members and contracting and publication service costs, but excluding that for staff support, is $1,500,000. The estimated annual person years of staff support from the Office for the Protection from Research Risk is six, at an estimated annual cost of $500,000.

Reports

Reports by the National Bioethics Advisory Commission on specific issues shall be submitted to the National Science and Technology Council, the appropriate committees of Congress, and other appropriate entities. The Commission may specifically identify the Federal department, agency or other entity to which particular recommendations are directed and request a response from the Federal department, agency or other entity within 180 days of publication of such recommendation.

Executive summaries of each report of the Commission shall be promulgated in the *Federal Register*. Such summaries shall specifically list the department, agency, or other entity to which any recommendations are directed and the date by which such responses are expected.

An annual report shall be submitted to the National Science and Technology Council and the appropriate committees of Congress. It shall contain, at a minimum, (i) the Commission's function; (ii) a list of members and their business addresses; (iii) the dates and places of meetings; (iv) a summary of the Commission's activities during the year; (v) a summary of the Commission's recommendations made during the year; and (vi) a summary of responses made by departments, agencies, or other entities to the Commission's recommendations during the year.

Termination Date

Unless renewed by appropriate action prior to its expiration, this National Bioethics Advisory Commission will terminate two years from the date this charter is approved.

Glossary

Terms Associated With Human Subjects Research

Abuse-Liable

Pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both illicit drugs (e.g., heroine) and licit drugs (e.g., methamphetamines).

ADAMHA (Alcohol, Drug Abuse and Mental Health Administration)

Reorganized in October 1992 as the Substance Abuse and Mental Health Services Administration (SAMHSA). ADAMHA included the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), the Office for Substance Abuse Prevention (OSAP), and the Office for Treatment Intervention (OTI). NIMH, NIAAA, and NIDA are now part of the National Institutes of Health (NIH). *(See also: Substance Abuse and Mental Health Services Administration (SAMHSA)).*

Adjuvant Therapy

Therapy provided to enhance the effect of a primary therapy; auxiliary therapy.

Adverse Event

An undesirable or unintended, although not necessarily unexpected, result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy).

Alpha Radiation

See: Ionizing radiation.

Assent

Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Association

In statistics, the correlation or relationship between one factor and one or more other pertinent factors as demonstrated by experimental data.

Assurance

A formal, written statement submitted to a Federal agency in which an institution promises to comply with applicable rules governing research with human subjects. An assurance covers all research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States. Assurances applicable to federally supported or conducted research shall include at a minimum: (1) a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects or research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation; (2) designation of one or more IRBs established in accordance with the requirements of 10 CFR 745; (3) a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, and employment or other

relationship between each member and the institution; (4) written procedures that the IRB will follow; and (5) written procedures for ensuring prompt reporting to the IRB. There are two types of assurances: single project and multiple project.

Atomic Bomb An explosive device in which a large amount of energy is released through the nuclear *fission* of uranium or plutonium. The first atomic bomb test, known as the Trinity Shot, took place in the desert north of Alamogordo, New Mexico, on 16 July 1945. Several weeks later, the bomb was used for the first time as an instrument of war, detonating over the Japanese cities of Hiroshima (August 6) and Nagasaki (August 9).

Atomic Pile *See: Nuclear reactor.*

Audit A formal inspection by a cognizant Federal agency of an institution's policies, procedures, and practices on the conduct of research involving human subjects and its associated IRB activities to determine compliance with applicable Federal regulations. Inspections may be either of a surveillance nature or conducted "for cause."

Authorized Institutional Official An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the Federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

Autonomy Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

Autopsy Examination by dissection of the body of a deceased individual to determine the cause of death and other medically relevant facts.

Becquerel *See: Units of radioactivity.*

Belmont Report A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

Beneficence An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

Benefit A valued or desired outcome; an advantage; something that promotes or protects well-being.

Beta Radiation *See: Ionizing radiation.*

Biodistribution The pattern and process of a chemical substance's distribution through the body.

Bioethics — The study of moral values in the life sciences and in their clinical applications. Emerging in the 1960s as a contemporary discipline, bioethics has ancient roots in medical ethics.

Biologic — Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

Biopsy — The removal and/or examination of tissues, cells, or fluids from a living body for the purposes of diagnosis or other experimental tests.

Biophysics — A science involving the application of physical principles and methods to study and explain the structures of living organisms and the mechanics of life processes.

Blind Study Designs — *See: Masked Study Designs; Double-Masked Design; and Single-Masked Design.*

Body Burden — The amount of a radioactive material present in a body, commonly used in reference to *radionuclides* having a long biological *half-life.* A body burden that subjects the body's most sensitive organs to the highest dose of a particular *radionuclide* that regulators allow is know as a *Maximum Permissible Body Burden (MPBB).*

Bone Marrow Infusion — The injection of bone marrow (an essential tissue producing red and white blood cells and platelets) into the body, used primarily to replace bone marrow destroyed in the course of *radiation* and other *therapies* for certain types of cancer.

Carcinogen — A material that can initiate or promote the development of cancer. Well-known carcinogens include saccharine, certain pesticides, and *ionizing radiation.*

Cadaver — The body of a deceased person.

Case-Control Study — A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. *(See also: Retrospective Studies.)*

CAT Scan — Abbreviation for Computerized Axial Tomography, an x-ray technique for producing images of internal bodily structures through the assistance of a computer.

CDC (Centers for Disease Control and Prevention) — A Federal agency within the Public Health Service, Department of Health and Human Services.

Certification — The official notification by the institution to the supporting department or agency, in accordance with the requirements of 10 CFR Part 745, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

CFR (Code of Federal Regulations) — A compendium of rules issued by Federal agencies on a multiplicity of topics.

Chain Reaction — The process by which the *fission* of a nucleus releases neutrons, causing other nuclei to undergo fission in turn. Both the *atomic bomb* and the *nuclear reactor* use a chain reaction to generate energy.

Children — Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.401(a)].

Class I, II, III Devices — Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.

Clinical Trial — A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices or of behavioral interventions.

Cognitively Impaired — Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons 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, may also be compromised in their ability to make decisions in their best interests.

Cohort — A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.

Compensation — Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research. *(Compare: Remuneration.)*

Competence — Technically, a legal term used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. *(See also: Incompetence, Incapacity.)*

Compliance — Means that an institution promises to comply with applicable rules governing research with human subjects.

Confidentiality — Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

Consent — *See: Informed Consent.*

Continuing Review — Review by the IRB of previously approved research; conducted at intervals appropriate to the degree of risk but not less than once per year.

Contract — An agreement; as used here, an agreement that a specific research activity will be performed at the request, and under the direction, of the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant. *(Compare: Grant.)*

Contraindicated — Disadvantageous, perhaps dangerous; a treatment that *should not be* used in certain individuals or conditions due to risks (e.g., a drug may be contraindicated for pregnant women and persons with high blood pressure).

Control (Subjects) or Controls — Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with *their own* condition on a prior regimen or treatment, the study is considered historically controlled.

Cooperative Research — Projects involving one or more institutions, each of which is responsible for safeguarding the rights and welfare of human subjects.

Correlation Coefficient — A statistical index of the degree of relationship between two variables. Values of correlation coefficients range from -1.00 through zero to + 1.00. A correlation coefficient of 0.00 indicates no relationship between the variables. Correlations approaching -1.00 or +1.00 indicate strong relationships between the variables. However, causal inferences about the relationship between two variables can never be made on the basis of correlation coefficients, no matter how strong a relationship is indicated.

Critical Mass — The amount of fissionable material (uranium-235 or plutonium-239) sufficient to sustain a nuclear *chain reaction.*

Cross-Over Design — A type of clinical trial in which each subject experiences, at different times, both experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the other half would have the sequence reversed.

Curie — *See: Units of radioactivity.*

Cyclotron — A device that uses electric and magnetic fields to accelerate subatomic particles (a particle smaller than an atom, such as an alpha particle or a proton). When these particles strike ordinary nuclei, *radioisotopes* are formed. For his work in developing the cyclotron in the early 1930s, Ernest Lawrence of the University of California received the 1939 Nobel Prize in Physics.

Data and Safety Monitoring Board — A committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that

would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

Dead Fetus — An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) [45 CFR 46.203(f)]. Generally, some organs, tissues, and cells (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

Debriefing — Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)

Declaration of Helsinki — A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

Dependent Variables — The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).

Descriptive Study — Any study that is not truly experimental (e.g., quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).

Device (medical) — *See: Medical Device.*

DHEW (U.S. Department of Health, Education and Welfare) — A Federal agency; reorganized in 1980 as the Department of Health and Human Services (DHHS) and the Department of Education.

DHHS (U.S. Department of Health and Human Services) — A Federal agency; formerly the Department of Health, Education and Welfare (DHEW). Agency includes the Food and Drug Administration; Centers for Disease Control and Prevention; National Institutes of Health; Alcohol, Drug Abuse and Mental Health Administration.

Diagnostic (Procedure) — Tests used to identify a disorder or disease in a living person.

Dosage — The prescribed amount of medicine or other *therapeutic* agent administered to treat a given illness.

Dose — In radiology, a measure of energy absorbed in the body from *ionizing radiation,* measured in *rads.*

Dose Reconstruction — The process of using information about an individual's past exposures to *ionizing radiation* as well as general knowledge about the behavior of *radioactive* materials in the human body and in the environment to estimate the *dose* of *radiation* that someone has received.

Dosimeter An instrument that measures exposure to *ionizing radiation.* A *biological dosimeter* is a biological or biochemical indicator of exposure, such as a change in blood chemistry or in blood count. A highly accurate *biological dosimeter* has yet to be found.

Dosimetry The measurement of *radiation doses.*

Double-Blind Design *See: Double-Masked Design.*

Double-Masked Design A study design in which neither the investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as "double-blind."

Drug Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

Emancipated Minor A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. *(See also: Mature Minor.)*

Embryo Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy). *(See also: Fetus.)*

Emergency Care Medical care provided 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. The investigator is still required to obtain informed consent under these circumstances.

Endocrinology The study of the body's hormone-producing glands, such as the thyroid, pituitary, and adrenal glands, and the functions of the hormones they synthesize and secrete.

Epidemiology A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or given population.

Equitable Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.

Ethics Advisory Board An interdisciplinary group that advises the DHHS Secretary on general policy matters and on research proposals (or classes of proposals) that pose ethical problems.

Ethnographic Research Ethnography is the study of people and their culture. Ethnographic research, also called fieldwork, involves observation of and interaction with the persons or group being studied in the group's own environment, often for long periods of time. *(See also: Fieldwork.)*

Expanded Availability Policy and procedure that permits individuals who have serious or life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them. Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.

Expedited Review Review of proposed research by the IRB chairperson or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

Experimental Term often used to denote a therapy (drug, device, procedure, etc.) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal study (research) to evaluate its usefulness. *(See also: Research.)*

Experimental Study A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation. *(See also: Quasi-Experimental Study).*

Fallout *Radioactive* debris that falls to earth after a nuclear explosion.

False Negative When a test wrongly shows an effect or condition to be absent (e.g., that a woman is *not* pregnant when, in fact, she is).

False Positive When a test wrongly shows an effect or condition to be present (e.g., that a woman *is* pregnant when, in fact, she is not).

FDA (Food and Drug Administration) An agency of the Federal Government established by Congress in 1912 and presently part of the Department of Health and Human Services.

Federal Policy (The) The Federal policy that provides regulations for the involvement of human subjects in research. The Policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the Policy applicable to such research. Currently, 16 Federal agencies have adopted the Federal Policy. (Also known as the "Common Rule.")

Fetal Material The placenta, amniotic fluid, fetal membranes, and umbilical cord.

Fetus The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)]. The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development. *(See also: Embryo.)*

Field Research A behavioral, social, or anthropological study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings).

Fieldwork — Behavioral, social, or anthropological research involving the study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings). *(See also: Ethnographic Research.)*

Fission — The division of an atomic nucleus into parts of comparable mass. Generally speaking, fission may occur only in heavier nuclei, such as *isotopes* of uranium, plutonium, and thorium. *Atomic bombs* derive energy from the *fission* of uranium or plutonium.

Fission Product — An atom or nucleus that results from the *fission* of a larger nucleus.

510(k) Device — A medical device that is considered substantially equivalent to a device that was or is being legally marketed. A sponsor planning to market such a device must submit notification to the FDA 90 days in advance of placing the device on the market. If the FDA concurs with the sponsor, the device may then be marketed. 510(k) is the section of the Food, Drug and Cosmetic Act that describes premarket notification; hence the designation "510(k) device."

Foreign Research — When research involving human subjects takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in 10 CFR Part 745. 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 the Federal policy.

Full Board Review — Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

Fusion — The combining of two light atomic nuclei to form a single heavier nucleus, releasing energy. *Hydrogen bombs* derive a large portion of their energy from the fusion of hydrogen *isotopes.*

Gamma Radiation — *See: Ionizing radiation.*

General Assurance — Obsolete term, previously used to denote an institutional assurance covering multiple research projects. *(See also: Assurance.)*

General Controls — Certain FDA statutory provisions designed to control the safety of marketed drugs and devices. The general controls include provisions on adulteration, misbranding, banned devices, good manufacturing practices, notification and record keeping, and other sections of the Medical Device Amendments to the Food, Drug and Cosmetic Act [21 U.S. Code 360(c) (Food, Drug and Cosmetic Act 513)].

Gene Therapy — The treatment of genetic disease accomplished by altering the genetic structure of either somatic (nonreproductive) or germline (reproductive) cells.

Genetic Screening — Tests to identify persons who have an inherited predisposition to a certain genotype or who are at risk of producing offspring with diseases or disorders.

Genotype — The genetic constitution of an individual.

Grant — Financial support provided for research study designed and proposed by the principal investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant. *(Compare: Contract.)*

Guardian — An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(3)].

Half-life — The average time required for one-half of any quantity of a *radionuclide* to undergo *radioactive* decay. For material with a half-life of one week, half of the original amount will remain after one week; half of that (one-quarter of the original amount) will remain after two weeks; and so on.

Helsinki Declaration — *See: Declaration of Helsinki.*

Historical Controls — Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently. The study is considered historically controlled when the present condition of subjects is compared with their own condition on a prior regimen or treatment.

Human In Vitro Fertilization — Any fertilization involving human sperm and ova that occurs outside the human body.

Human Subjects — Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under Federal regulations, human subjects are defined as living individual(s) about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Hydrogen Bomb — An explosive weapon that uses nuclear *fusion* to release energy stored in the nuclei of hydrogen *isotopes*. The high temperatures essential to *fusion* are attained by detonating an *atomic bomb* placed at the h-bomb's structural center. The United States tested the first hydrogen bomb in 1954 at the Pacific Test Site. (Also known as a thermonuclear weapon.)

IDE (Investigational Device Exemptions) — Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations [21 CFR 812.20].

Incapacity — Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence. *(See also: Incompetence.)*

Incompetence Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity. *(See also: Incapacity.)*

IND (Investigational New Drug or Device) A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

Independent Variables The conditions of an experiment that are systematically manipulated by the investigator.

Individually Identifiable When the identity of the subject is or may readily be ascertained by the investigator or associated with the information. In order for a project to be considered research involving human subjects, private information collected from a subject must be individually identifiable.

Informed Consent A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventative procedure. The following information at a minimum must be included in informed consent forms provided to research subjects: (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 subjects 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 of whom to contact in the event of a research-related injury to the subject or for answers to pertinent questions about the research and research subjects' rights; and (7) a statement that participation is voluntary and that 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 entitled. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence [Federal Policy 116; 21 CFR 50.20 and 50.25].

Institution (1) Any public or private entity or agency (including Federal, state, and other agencies).

Institution (2) A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

Institutionalized — Confined, either voluntarily or involuntarily (e.g., a hospital, prison, or nursing home).

Institutionalized Cognitively Impaired (mentally disabled) — Persons who are confined, either voluntarily or involuntarily, in a facility for the care of the mentally or otherwise disabled (e.g., a psychiatric hospital, home, or school for the retarded).

Interaction — Interaction includes communication or interpersonal contact between investigator and subject.

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.

Invasive — Involving entry into the living body (as by incision or by insertion of an instrument).

Investigator — In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (e.g., drugs) involved in the study are administered to subjects under the immediate direction of the investigator. *(See also: Principal Investigator.)*

In Vitro — Literally, "in glass" or "test tube"; used to refer to processes that are carried out outside the living body, usually in cells, tissues, or fluids removed from a living body, as distinguished from in vivo.

In Vivo — Literally, "in the living body"; processes, such as the absorption of a drug by the human body, carried out in the living body rather than in cells, tissues, or fluids outside of a living body.

Ionization — The process by which a neutral atom or molecule loses or gains electrons, thereby acquiring a net electrical charge. When charged, it is known as an ion.

Ionizing Radiation — Any of the various forms of radiant energy that causes *ionization* when it interacts with matter. The most common types are *alpha radiation,* made up of helium nuclei; *beta radiation,* made up of electrodes; and *gamma* and *x-radiation,* consisting of high-energy particles of light (photons).

IRB (Institutional Review Board) — A formally constituted group of individuals responsible for reviewing all research covered by an assurance for a given institution. The IRB possesses the authority to approve, disapprove, suspend, or terminate previous approval of such research in order to protect the rights and welfare of human subjects. An 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. 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.

Irradiation — Exposure to *ionizing radiation.*

Isotope — A species of nucleus with a fixed number of protons and neutrons. The term *isotope* is usually used to distinguish nuclear species of the same chemical element (i.e., those having the same number of protons, but different numbers of neutrons), such as iodine-127 and iodine-131.

Justice — An ethical principle discussed in the Belmont Report requiring fairness in the distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

Lactation — The period of time during which a woman is providing her breast milk to an infant or child.

Latency Period — The time between when an exposure occurs and when its effects are detectable as an injury or illness.

Legally Authorized Representative — A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, 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.

LOD Score — An expression of the probability that a gene and a marker are linked.

Longitudinal Study — A study designed to follow subjects forward through time.

Masked Study Designs — Study designs comparing two or more interventions in which either the investigators, the subjects, or some combination thereof do not know the treatment group assignments of individual subjects. Sometimes called "blind" study designs. *(See also: Double-Masked Design, Single-Masked Design.)*

Mature Minor — Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. *(See also: Emancipated Minor.)*

MDA (Medical Device Amendments) — Amendments to the Federal Food, Drug and Cosmetic Act passed in 1976 to regulate the distribution of medical devices and diagnostic products.

Medical Device — A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, intrauterine contraceptive devices, diagnostic test kits, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

Mentally Disabled — Having either a psychiatric disorder (e.g., psychosis, neurosis, personality, or behavioral disorder), a developmental disorder (e.g., mental retardation), or a neurological disorder that affects cognitive or emotional functions to the extent

that capacity for judgment and reasoning is significantly diminished. *See: Cognitively Impaired.*

Metabolism (of a Drug) The manner in which a drug is acted upon (taken up, converted to other substances, and excreted) by various organs of the body.

Minimal Risk A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed 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 example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults. [*See* 45 CFR 46.303(d).]

Monitoring The collection and analysis of data as the project progresses to ensure the appropriateness of the research, its design, and subject protections.

MPBB (Maximum Permissible Body Burden) *See: Body burden.*

MRI (Magnetic Resonance Imaging) The use of strong magnetic fields and low-frequency (non-ionizing) electromagnetic *radiation* to produce images of structures inside the human body. Since the mid-1980s, MRI has become a common diagnostic technique, supplanting the CAT scan, which makes use of *ionizing radiation.*

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research An interdisciplinary advisory body established by congressional legislation in 1974 and in existence until 1978, which issued a series of reports and recommendations on ethical issues in research and medicine, many of which are now embodied in Federal regulations.

Natural Background Radiation *Ionizing radiation* that occurs naturally. Its principal sources are cosmic rays from outer space, *radionuclides* in the human body, and radon gas.

NDA (New Drug Application) Request for FDA approval to market a new drug.

NIH (National Institutes of Health) A Federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.

Nonaffiliated Member Member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (e.g., minister, business person, attorney, teacher, homemaker).

Noninvasive — Not involving penetration (as by surgery or hypodermic needle) of the skin or body of the intact organism.

Nonsignificant Risk Device — An investigational medical device that does not present significant risk to the patient. *(See also: Significant Risk Device.)*

Nontherapeutic Research — Research that has no likelihood or intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.

Nonviable Fetus — An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy [45 CFR 46.203 (d) and (e)]. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age of less than 20 weeks and a weight of less than 500 grams [Federal Register 40 (August 8, 1975): 33552], a specific determination as to viability must be made by a physician in each instance. *(See also: Viable Infant.)*

Normal Volunteers — Volunteer subjects used to study normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease.

Nuclear Medicine — A branch of medicine specializing in the use of *radionuclides* for diagnostic and therapeutic purposes.

Nuclear Reactor — A device containing *fissionable* material in sufficient quantity and suitable arrangement to maintain a controlled, self-sustaining nuclear *chain reaction.*

Nuclide — A type of nucleus with a fixed number of protons and neutrons. The term *nuclide* is usually used to distinguish nuclear species of different chemical elements (i.e., those having different numbers of protons and neutrons), such as iodine-127 and uranium-235.

Null Hypothesis — The proposition, to be tested statistically, that the experimental intervention has "no effect," meaning that the treatment and control groups will not differ as a result of the intervention. Investigators usually hope that the data will demonstrate some effect from the intervention, thereby allowing the investigator to reject the null hypothesis.

Nuremberg Code — A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

Occupational Health Surveillance — The standardized, ongoing collection of routinely gathered information covering a worker's pertinent demographics, medical findings, and occupational exposure history.

Open Design — An experimental design in which both the investigator(s) and the subjects know the treatment group(s) to which subjects are assigned.

OPRR (Office for Protection from Research Risks) — The office within the National Institutes of Health, an agency of the Public Health Service, Department of Health and Human Services, responsible for implementing DHHS regulations (45 CFR Part 46) governing research involving human subjects.

Paternalism — Making decisions for others against or apart from their wishes with the intent of doing them good.

PBI (Partial Body Irradiation) — Exposure of part of the body to external *radiation.*

Permissible Dose — In the judgement of a regulatory or advisory body, such as the National Committee on Radiation Protection, the amount of *radiation* that may be received by an individual within a specified period.

Permission — The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].

Pharmacology — The scientific discipline that studies the action of drugs on living systems (animals or human beings).

Phase 1, 2, 3, 4 Drug Trials — Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to postmarketing studies (Phase 4).

Phase 1 Drug Trial — Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20–80.

Phase 2 Drug Trial — Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

Phase 3 Drug Trial — Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained. They are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide and adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

Phase 4 Drug Trial — Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR 312.85].

Phenotype — The physical manifestation of a gene function.

PHS (Public Health Service) — Part of the U.S. Department of Health and Human Services, it includes FDA, NIH, CDC, SAMHSA, and HRSA.

PI (Principal Investigator) — The scientist or scholar with primary responsibility for the design and conduct of a research project. *(See also: Investigator.)*

Placebo — A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than the actual power of a drug.

Postamendments Devices — Medical devices marketed after enactment of the 1976 Medical Device Amendments.

Preamendments Devices — Medical devices marketed before enactment of the 1976 Medical Device Amendments.

Preclinical Investigations — Laboratory and animal studies designed to test the mechanisms, safety, and efficacy of an intervention prior to its applications to humans.

Predicate Devices — Currently legally marketed devices to which new devices may be found substantially equivalent under the 510(k) process.

Pregnancy — The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This "confirmation" may be in error, but for research purposes, investigators presume that a living fetus is present until evidence to the contrary is clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes necessary a definition of pregnancy based on implantation.

Premarket Approval — Process of scientific and regulatory review by the FDA to ensure the safety and effectiveness of Class III devices.

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research — An interdisciplinary advisory group, established by congressional legislation in 1978 and in existence until 1983, that issued reports on ethical problems in health care and in research involving human subjects.

Prisoner — An individual involuntarily confined in a penal institution, including persons (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution [45 CFR 46.303(c)].

Privacy — Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

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 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). 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.

Proband — The person whose case serves as the stimulus for the study of other members of the family to identify the possible genetic factors involved in a given disease, condition, or characteristic.

Prophylactic — Preventive or protective; a drug, vaccine, regimen, or device designed to prevent, or provide protection against, a given disease or disorder.

Prospective Studies Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.

Protocol The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

Purity The relative absence of extraneous matter in a drug or vaccine that may or may not be harmful to the recipient or deleterious to the product.

Quasi-Experimental Study A study that is similar to a true experimental study except that it lacks random assignments of subjects to treatment groups. *(See also: Experimental Study.)*

Rad *See: Units of radiation.*

Radiation Oncology Branch of medicine specializing in the treatment of cancer with *radiation.*

Radiation Sickness Acute physical illness caused by exposure to *doses* of *ionizing radiation* large enough to cause toxic reactions. This can include symptoms such as nausea, diarrhea, headache, lethargy, and fever.

Radioactive Drug Any substance defined as a drug in 201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons [21 CFR 310.3(n)]. Included are any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of a radioactive drug and "radioactive biological products," as defined in 21 CFR 600.3(ee). Drugs such as carbon-containing compounds or potassium-containing salts containing trace quantities of naturally occurring radionuclides are not considered radioactive drugs.

Radioactivity The decay of unstable nuclei through the emission of *ionizing radiation.* The resulting nucleus may itself be unstable, and undergo radioactive decay. The process stops only when the decay product is stable.

Radioisotope A *radioactive isotope.* Radioisotopes are used in medical research as *tracers.*

Radiological Weapons Weapons that use *radioactive* materials to cause *radiation* injury.

Radiopaque Contrast Agents Materials that stop or attenuate radiation that is passed through the body, creating an outline on film of the organ(s) being examined. Contrast agents, sometimes called "dyes," do not contain radioisotopes. When such agents are used, exposure to radiation results only from the x-ray equipment used in the examination. The chemical structure of radiopaque contrast agents can produce a variety of adverse

reactions, some of which may be severe—and possibly life-threatening—in certain individuals.

Radionuclide — A *radioactive nuclide.* Often used to distinguish *radioisotopes* of different chemical elements, such as iodine-131 and uranium-239.

Radiopharmaceuticals — Drugs (compounds or materials) that may be labeled or tagged with a radioisotope. These materials are largely physiological or subpharmacological in action, and in many cases function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are injected into the body.

Radioresistance — The degree of resistance of organisms or tissues to the harmful effects of *ionizing radiation.*

Radiosensitivity — The degree of sensitivity of organisms or tissues to the harmful effects of *ionizing radiation.*

Random, Random Assignment, Randomization, Randomized — Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

RDRC (Radioactive Drug Research Committee) — An institutional committee responsible for the use of radioactive drugs in human subjects for research purposes. Research involving human subjects that proposes to use radioactive drugs must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug use to ensure that the research continues to comply with FDA requirements, including reporting obligations. The committee must include experts in nuclear medicine and the use of radioactive drugs, as well as other medical and scientific members [21 CFR 36.1].

Recombinant DNA Technology — "The ability to chop up DNA, the stuff of which genes are made, and move the pieces, [which] permits the direct examination of the human genome," and the identification of the genetic components of a wide variety of disorders [Holtzman (1989), p. 1]. Recombinant DNA technology is also used to develop diagnostic screens and tests, as well as drugs and biologics for treating diseases with genetic components.

REM — Abbreviation for Roentgen Equivalent in Man; the unit of measurement for a dose of an ionizing radiation that produces the same biological effect as a unit of absorbed radiation (1 rad) of ordinary x-rays. One millirem is equal to 1/1000 of a rem.

Remission — A period in which the signs and symptoms of a disease are diminished or in abeyance. The term "remission" is used when one cannot say with confidence that the disease has been cured.

Remuneration — Payment for participation in research. (NOTE: It is wise to confine use of the term "compensation" to payment or provision of care for research-related injuries.) *(Compare: Compensation.)*

Rep — *See: Units of radiation.*

Research — A systematic investigation (i.e., the gathering and analysis of information) designed to develop or contribute to generalizable knowledge.

Respect for Persons — An ethical principle discussed in the Belmont Report requiring that individual autonomy be respected and that persons with diminished autonomy be protected.

Retrospective Studies — Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case-control studies are an example of this type of research.

Review (of research) — The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by Federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis.

Risk — The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk." *(See also: Minimal Risk.)*

Roentgen — *See: Units of radiation.*

SAMHSA (Substance Abuse and Mental Health Services Administration) — Includes the Center for Substance Abuse Prevention, the Center for Substance Abuse Treatment, and the Center on Mental Health Services. Previously, the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). *(See also: ADAMHA.)*

Scientific Review Group — A group of highly regarded experts in a given field, convened by NIH to advise NIH on the scientific merit of applications for research grants and contracts. Scientific review groups are also required to review the ethical aspects of proposed involvement of human subjects. Various kinds of scientific review groups exist, and are known by different names in different institutes of the NIH (e.g., Study Sections, Initial Review Groups, Contract Review Committees, or Technical Evaluation Committees).

Side Effect — An unwanted effect produced by a drug in addition to its desired therapeutic effects. Side effects are often undesirable and may be harmful.

Significant Risk Device An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject.

Single-Blind Design Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally, it is the subject, and not the investigator, who knows the assignment.

Single-Masked Design Typically, a study design in which the investigator, but not the subject, knows the identity of the treatment assignment. Occasionally, it is the subject, and not the investigator, who knows the assignment. Sometimes called "single-blind design."

Site Visit A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

Social Experimentation Systematic manipulation of, or experimentation in, social or economic systems; used in planning and public policy.

Sponsor Agency funding a research project.

Sponsor-Investigator An individual who both initiates and actually conducts, alone or with others, a clinical investigation. Corporations, agencies, or other institutions do not qualify as sponsor-investigators.

Sponsor (of a Drug Trial) A person or entity that initiates a clinical investigation of a drug—usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation, but rather distributes the new drug to investigators and physicians for clinical trials. The drug is administered to subjects under the immediate direction of an investigator who is not also a sponsor. A clinical investigator may, however, serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

Statistical Significance The probability that two treatments or conditions under study are really different as opposed to the likelihood that any variations observed have resulted by chance. By consensus, if there is less than a 1 in 20 possibility that observed differences occurred by chance, the results are said to be statistically significant (at the .05 level of confidence). If the possibility that the differences resulted from chance is 1 in 100, the results are said to be statistically significant at the .01 level of confidence. If the results are statistically significant, the null hypothesis is rejected.

Sterility (1) The absence of viable contaminating microorganisms; aseptic state.

Sterility (2) The inability to procreate; the inability to conceive or induce conception.

Study Section — A scientific review group, conveyed by the NIH from among highly regarded experts in a given field, that advises on the scientific merit of applications for research grants and contracts. Study sections are also required to review ethical aspects of proposed use of human subjects. *(See also: Scientific Review Group.)*

Subjects (Human) — *See: Human Subjects.*

Surveys — Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

TBI (Total Body Irradiation — Exposure of the entire body to external *radiation.*

Therapeutic Intent — The research physician's intent to provide some benefit to improving a subject's condition (e.g., prolongation of life, shrinkage of tumor, or improved quality of life, even though cure or dramatic improvement cannot necessarily be effected.) This term is sometimes associated with Phase 1 drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition as well as assessing the safety and pharmacology of a drug.

Therapeutic Research — Research involving an intervention that has the likelihood of providing a therapeutic, diagnostic, or preventative benefit to the subjects.

Therapy — Treatment intended and expected to alleviate a disease or disorder.

Tolerance Dose — *See: Permissible dose.*

Tracer — A distinguishable substance, usually *radioactive,* administered to determine the distribution and/or *metabolism* of materials in the body. In 1923, George Hevesy was the first investigator to use an *isotope* (radioactive thorium) in metabolic studies, exploring lead transport in the bean plant. Metabolic studies proliferated after World War II, when with the development of the *cyclotron, radioisotopes* of various atoms became more widely available. *Isotopes* commonly used as *tracers* today include carbon-14, iodine-131, and phosphorous-32.

Transuranic Elements — Radioactive elements with atomic numbers (i.e., protons) greater than 92. Only two of these elements (neptunium and plutonium) occur in nature; the others are produced in minute amounts through the radioactive decay of uranium. The first *transuranic elements* were discovered as synthetic *radioisotopes* at the University of California at Berkeley and the Argonne National Laboratory in the 1930s and 1940s.

Uniform Anatomical Gift Act — Legislation adopted by all 50 states and the District of Columbia that indicates procedures for donation of all or part of a decedent's body for activities such as medical education, scientific research, and organ transplantation.

Units of Radiation

The basic unit of *radiation* exposure is the *roentgen,* a measure of *ionization* in air, technically equal to one ESU (electrostatic unit) per cubic centimeter. A *rep* is an archaic measure of skin exposure to *beta radiation,* equivalent to one *roentgen.* The basic unit of *radiation* absorbed by the body is the *rad,* technically equal to one hundred ergs (energy unit) per gram of exposed tissue. One *roentgen* corresponds to roughly 0.95 *rad.* The *rem (roentgen* equivalent in man) is a unit of effective dose, a dose corrected for the varying biological effectiveness of various types of *ionizing radiation.*

Units of Radioactivity

The *Becquerel (BQ),* named after the physicist Henri Becquerel, is a measure of radioactivity equal to one atomic disintegration per second. The *Curie (Ci),* whose name honors the French scientists Marie and Pierre, is a standard based on the radioactivity of 1 gram of radium. It is equal to 3.7×10^{10} *Becquerels.*

Vaccine

A biologic product generally made from an infectious agent or its components—a virus, bacterium, or other microorganism—that is killed (inactive) or live-attenuated (active, although weakened). Vaccines may also be biochemically synthesized or made through recombinant DNA techniques.

Variable

An element or factor that the research is designed to study—either as an experimental intervention or a possible outcome (or factor affecting the outcome) of that intervention.

Venipuncture

The puncture of a vein for any therapeutic purpose; for example, to extract blood for laboratory tests.

Viable Infant

When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy [45 CFR 46.203(d)]. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975 and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability [Federal Register 40 (August 8, 1975): 33552]. These indices depend on the state of present technology and may be revised periodically. *(See also: Nonviable Fetus.)*

Voluntary

Free of coercion, duress, or undue inducement; used in research context to refer to a subject's decision to participate (or continue participation) in a research activity.

X-rays

Invisible, highly penetrating electromagnetic *radiation* of a much shorter wavelength than visible light, discovered in 1895 by Wilhelm C. Roentgen. Most applications of X-rays are based on their ability to pass through matter. They are dangerous in that they can destroy living tissue, causing severe skin burns on human flesh exposed for too long a time. This property is applied in X-ray *therapy* to destroy diseased cells. *(See also: Ionizing radiation.)*

Additional References

Associations

The Applied Research Ethics National Association (ARENA) is a national service organization for researchers, administrators, institutional review board members, and other professionals interested in biomedical ethics. To obtain more information, write or call—

ARENA
132 Boylston Street
Boston, MA 02116
(617) 423-4112; F (617) 423-1185

Public Responsibility in Medicine and Research (PRIM&R) holds conferences related to various topics in human subjects and animal research. PRIM&R publishes comprehensive summaries of its conferences and provides educational packets. To obtain a listing and order form of conference summaries and educational packets, write or call—

PRIM&R
132 Boylston Street
Boston, MA 02116
(617) 423-4112; F (617) 423-1185

Databases

The primary information source related to human subjects research concerns is—

Bioethicsline, a National Library of Medicine (NLM) online bibliographical database covering the literature of the health sciences, law, religion, philosophy, the social sciences, and the popular media. Produced by the Information Retrieval Project at the Kennedy Institute of Ethics, Georgetown University, and supplied to the NLM MEDLARS system at the National Institutes of Health. Updated bi-monthly. To order free bibliographical computer searches, call the National Reference Center for Bioethics Literature, Kennedy Institute of Ethics, Georgetown University, at (800) 633-3849.

Bioethics Online Service: The Center for the Study of Bioethics at the Medical College of Wisconsin publishes the Bioethics Online Service which is free and can be reached by anyone with Internet access. Here's how to reach the Bioethics Online Service—

World Wide Web, Cello, Lynx, Win/MacWeb/Mosiac Uniform Resource Locator (URL):
gopher://post.its.mcw.edu:72/
telnet://min.lib.mcw.edu
http://www.mcw.edu/bioethics

Internet gopher:
Type gopher post.its.mcw.edu<enter>.

Internet telnet:
Type telnet min.lib.mcw.edu<enter>.
Choose the Bioethics Online Service from the menu.

Modem (any speed) and telephone line:
Dial (414) 266-5777.
At the prompt (MCW>) type c min<enter>.
Choose the Bioethics Online Service from the menu.

If you have any questions about log-in procedures, send e-mail to: biohelp@its.mcw.edu or call the Bioethics Online Service Technical Support at MCW Information Technology Systems, (414) 456-8700.

Other medical or social sciences databases available through commercial or government systems may provide useful references. To obtain online access, contact the National Library of Medicine MEDLARS Service at (800) 638-8480 or Internet e-mail, mmm@nlm.nih.gov.

Guidebooks/Manuals

The OPRR *1993 Protecting Human Research Subjects Institutional Review Board Guidebook.* Prepared by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, this publication consists of the following: background, regulations and commentary, administration of an IRB, research goals and procedures, considerations of research design, basic IRB review, special classes of subjects, forms, local IRB organizational documents, and a glossary of terminology. To obtain a copy, contact the Office for Protection from Research Risks, National Institutes of Health at (301) 496-7005.

U.S. Congress, Office of Technology Assessment, *Biomedical Ethics in U.S. Public Policy—Background Paper,* OTA-BP-BBS-105, Washington, DC: U.S. Government Printing Office, June 1993.

Instructional Aids

Clouser, K. Danner. *Teaching Bioethics: Strategies, Problems, and Resources.* Hastings-on-Hudson, NY: The Hastings Center, 1980.

Dax's Case: Who Should Decide?, an hour-long film of the burn patient discussed in the case study, "A Demand to Die." Produced by Concern for Dying and available from Filmakers Library, 124 E. 40th, New York, NY 10016, (212) 355-6545.

Food and Drug Administration (FDA) Information Sheets for Institutional Review Boards and Clinical Investigators. To obtain copies, contact the Health Assessment Policy Staff, Office of Health Affairs, U.S. Food and Drug Administration, 5600 Fishers Lane, Room 15-22 (HFY-20), Rockville, MD 20857 [telephone (301) 443-1382]. Updated information sheets will soon be available through the FDA home page on the Internet World Wide Web (http://www.fda.gov).

"Managing our Miracles: Health Care in America," a series of videotaped programs on a variety of topics in bioethics. Produced by Columbia University Seminars on Media and Society, 475 Riverside Drive, Suite 248, New York, NY 10115.

Reading packets on various subjects in bioethics, such as organ transplantation and forgoing food and fluids, are produced and distributed by The Center for Biomedical Ethics, University of Minnesota, UMHC Box 33, Harvard St. at E. River Road, Minneapolis, MN 55455.

Reports of the New York State Task Force on Life and the Law (e.g., on *Surrogate Parenting, Do Not Resuscitate Orders, Life-Sustaining Treatment, Transplantation in New York State)* may be obtained by writing to the task force at 33 West 34th St., 3rd floor, New York, NY 10001–3071.

International Codes

The Nuremberg Code. Reprinted in *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10,* vol. 12:81–82. Washington, DC: U.S. Government Printing Office, 1949; also printed in Medical Research Council of Canada, *Ethics in Human Experimentation,* pp. 59–60, 1978.

World Health Organization and the Council for International Organizations of Medical Sciences. *Proposed International Guidelines for Biomedical Research Involving Human Subjects.* Geneva: Council for International Organizations of Medical Sciences, 1982.

National Guidelines

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles for the Protection of Human Subjects of Research.* Washington, DC: U.S. Government Printing Office, 1978. Department of Health, Education and Welfare (now Health and Human Services), publication #(OS) 78–0012, Appendix 1–0013, Appendix 2–004.

_____. *Disclosure of Research Information Under the Freedom of Information Act.* Washington, DC: U.S. Government Printing Office, 1977. DHEW #(OS) 77–0011.

_____. *Report and Recommendations: Ethical Guidelines for the Delivery of Health Services for DHEW.* Washington, DC: U.S. Government Printing Office, 1978. DHEW #(OS) 78–0011.

_____. *Report and Recommendations: Institutional Review Boards.* Washington, DC: U.S. Government Printing Office, 1978. DHEW #(OS) 78–0011, Appendix–0009.

_____. *Report and Recommendations: Psychosurgery.* Washington, DC: U.S. Government Printing Office, 1977. DHEW #(OS) 77–0001.

_____. *Report and Recommendations: Research Involving Children.* Washington, DC: U.S. Government Printing Office, 1977. DHEW #(OS) 77–0004.

_____. *Report and Recommendations: Research Involving Prisoners.* Washington, DC: U.S. Government Printing Office, 1976. DHEW #(OS) 76–131.

_____. *Report and Recommendations: Research Involving Those Institutionalized as Mentally Infirm.* Washington, DC: U.S. Government Printing Office, 1978. DHEW #(OS) 78–0006.

_____. *Report and Recommendations: Research on the Fetus.* Washington, DC: U.S. Government Printing Office, 1975. DHEW #(OS) 776–127, Appendix–128.

_____. *Special Study: Implication of Advances in Biomedical and Behavioral Research.* Washington, DC: U.S. Government Printing Office, 1978. DHEW #(OS) 78–0015.

Newsletters/Periodicals

(The) American Journal of Law and Medicine.

(The) American Journal of Nursing.

Annals of Internal Medicine.

Archives of Internal Medicine.

ARENA distributes a quarterly newsletter that highlights upcoming conferences and regional news and provides a networking bulletin. If you are interested in joining ARENA or in receiving its quarterly newsletter, write or call ARENA, 132 Boylston Street, Boston, MA 02116. (617) 423-4112.

Bioethics (published in England, edited in Australia).

Bio-Law: A Legal and Ethical Reporter on Medicine, Health Care, and Bioengineering. Childress, James F., and Ruth D. Gaare (eds.) Frederick, MD: University Publications of America. Monthly updates of cases on 14 different topics in bioethics.

Canadian Journal of Philosophy.

Ethics.

Harvard Law Review.

Hastings Center Report (six times yearly). Published by the Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510.

IRB: A Review of Human Subjects Research (six times yearly). Published by the Hastings Center, 255 Elm Road, Briarcliff Manor, NY 10510.

IRC Info, a newsletter from Independent Review Consulting, provides news and topics of interest in human subjects research. For more information, write or call Erica Heath, 305 San Anselmo Avenue, Suite 305, San Anselmo, CA 94960, (415) 485-0717.

Journal of (the) American Medical Association (JAMA).

Journal of Health Politics, Policy and Law.

Journal of Medical Ethics (published in England).

Journal of Medicine and Philosophy.

Journal of Religious Ethics.

Lancet (British).

Law, Medicine and Health Care.
Linacre Quarterly.
Medical Humanities Review.
Milbank Quarterly (often publishes excellent supplementary issues devoted to such topics as AIDs and decision making for the elderly).
New England Journal of Medicine.
Nursing Research.
Pediatrics.
Perspectives in Biology and Medicine.
Philosophy and Public Affairs.
Social Theory and Practice.
Theological Studies.
Theoretical Medicine.
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Videotapes

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