NIH Human Research Protection Program

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A. PURPOSE

This policy establishes responsibilities and procedures for protecting the rights and safeguarding the welfare of human subjects who participate in research conducted or supported by the Intramural Research Program (IRP) of the National Institutes of Health (NIH).

B. BACKGROUND

In 1974 the U.S. Department of Health, Education and Welfare (DHEW, renamed Department of Health and Human Services {DHHS}) promulgated Federal regulations for the protection of human subjects. At the same time, Congress enacted the National Research Act, which mandated Institutional Review Board (IRB) review for all Public Health Service-funded research, and authorized the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("National Commission"). The law directed the National Commission to evaluate and make recommendations to the Secretary of DHEW about protecting human research subjects.

The National Commission evaluated the existing DHEW system for protecting human subjects, recommended improvements to the Secretary, DHEW, and issued separate reports and recommendations for research involving, among others, fetuses, prisoners, children, the mentally infirm and the use of psychosurgery. In 1979 the National Commission published *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research* ("*The Belmont Report*"). *The Belmont Report* is widely regarded today as a seminal report on the ethical principles for human subjects research. It provides guidance for distinguishing therapeutic medicine from research, identifies three fundamental ethical principles for the protection of human subjects (respect for persons, beneficence, justice), and shows how these ethical principles apply to the conduct of human research. These principles continue to provide the ethical foundation for conducting research with human subjects.

In 1979, DHEW began revising the 1974 regulations for the protection of human subjects, and in 1981 final Department approval was given to 45 CFR 46, Subparts A, B and C. On March 18, 1983, Subpart D was added to the regulations, providing additional protections for children who are subjects in research. Initially the DHHS regulations applied only to research conducted or supported by DHHS. But, in June 1991, the United States published a common policy for federal agencies conducting or supporting research with human subjects. That policy, which is known as "the Common Rule," extended the

provisions of 45 CFR Part 46, Subpart A, to fourteen other federal agencies; it now governs most federally-supported research.

C. POLICY

The NIH's mission is to improve human health through biomedical and behavioral research. The NIH's IRP has a Human Research Protection Program (HRPP) to protect the rights and safeguard the welfare of human subjects who participate in its research studies. The NIH HRPP endorses the following goals:

1. The NIH performs clinical research according to the highest scientific and ethical standards and in a manner that promotes and respects the rights and welfare of all human subjects.

2. The NIH ensures that the performance of all research involving human subjects conducted in the IRP complies with applicable Federal laws.

3. The NIH complies with *The Standards for Clinical Research within the NIH IRP* ("*The Standards"*). *The Standards* provide a detailed description of the clinical research infrastructure and resources each Institute is expected to provide in the areas of clinical informatics, data management, protocol tracking, biostatistics, quality assurance and quality control, protocol review, human resources, physical plant, training and education. *The Standards* can be found at http://www.cc.nih.gov/ccc/clinicalresearch/index.html .

4. The NIH requires its investigators to understand the regulatory definition of research with human subjects and to know when they are conducting human subjects research.

5. The NIH IRP, in cooperation with the Institutes and Centers (ICs), establishes and maintains Institutional Review Boards (IRBs). These IRBs are responsible for the prospective and continuing review and approval of research activities involving human subjects. Their primary mandate is to protect the rights and safeguard the welfare of human research subjects. The composition and operation of each IRB conforms to the terms and conditions of 45 CFR Part 46.

6. NIH IRBs review research protocols only after they have been reviewed by the applicable IC and found to be scientifically meritorious.

7. The NIH ensures that the IRBs exercise independent authority and decision-making with respect to the review and approval of human subjects research.

D. COVERAGE

The IRP consists of separately funded programs that operate in the following ICs of the NIH:

1. National Institute on Alcohol Abuse and Alcoholism (NIAAA).

2. National Institute of Allergy and Infectious Diseases (NIAID), including the Rocky Mountain Laboratory, Hamilton, Montana.

3. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), including NIAMS activities at the Cardozo Clinic in Washington, D.C.

4. National Institute of Biomedical Imaging and Bioengineering (NIBIB).

5. National Cancer Institute (NCI), including the Frederick Cancer Research and Development Center, Frederick, Maryland.

6. National Institute of Child Health and Human Development (NICHD), including the Perinatology Research Branch, Wayne State University, Hutzel Hospital, Detroit, Michigan.

7. National Institute of Deafness and other Communication Disorders (NIDCD).

8. National Institute of Dental and Craniofacial Research (NIDCR).

9. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including the Phoenix Epidemiology and Clinical Research Branch, Phoenix, Arizona.

10. National Institute on Drug Abuse (NIDA), Baltimore, Maryland.

11. National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.

12. National Eye Institute (NEI).

13. National Heart, Lung and Blood Institute (NHLBI).

14. National Human Genome Research Institute (NHGRI), including the Center for Inherited Disease Research in Baltimore, Maryland.

15. National Institute of Mental Health (NIMH).

16. National Institute of Neurological Disorders and Stroke (NINDS).

17. National Institute of Nursing Research (NINR).

18. National Center for Complementary and Alternative Medicine (NCCAM).

19. The clinical center research complex, including the Warren Grant Magnuson Clinical Center and the Mark O. Hatfield Clinical Research Center.

20. The National Institute on Aging (NIA).

The NIA's primary clinical research site, located at the Harbor Hospital in Baltimore, Maryland, follows Harbor Hospital's policies and procedures for the protection of human subjects. Harbor Hospital is part of the Medstar Research Institute, which has its own FWA. (A Federal Wide Assurance, referred to commonly as an "FWA" is defined in Section F of this Manual Chapter.)

E. REFERENCES: See Appendix 1

The ethical principles, regulations, policies and guidelines that apply to the conduct of research in the IRP are set forth in Appendix 1.

F. DEFINITIONS

1. ***HUMAN SUBJECT*** means a living individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual, or (b) identifiable private information (45 CFR 46.102(f)). Some clinical and basic research activities with human tissues (i.e., blood and tissue samples) may also be considered research involving human subjects.

2. ***RESEARCH*** means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102(e)).

3. ***LEGALLY AUTHORIZED REPRESENTATIVE*** means an individual, 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 (45 CFR 46.102 (c)).

4. ***A CHILD*** is a person who has 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. (45 CFR 46.402).

5. ***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 (45 CFR 46.102 (i)).

6. ***INSTITUTIONAL REVIEW BOARD (IRB)*** is a committee established in accord with, and for the purposes set forth in 45 CFR 46 and/or 21 CFR 56. The Food and Drug Administration regulations (21 CFR 56) are similar to 45 CFR 46, Subpart A. The mandate of IRBs is to protect the rights and safeguard the welfare of human research participants.

7. ***THE OFFICE OF HUMAN SUBJECTS RESEARCH (OHSR)*** is within the Office of Intramural Research (OIR), NIH. OHSR helps NIH investigators and staff understand and comply with ethical principles and regulatory requirements for the protection of human research subjects. The OHSR website is http://ohsr.od.nih.gov/

8. ***THE OFFICE OF HUMAN RESEARCH PROTECTIONS (OHRP)*** is within the Office of Public Health and Science in the Office of the Secretary, DHHS. OHRP provides leadership on human research subject protections and implements a program of compliance oversight for DHHS regulations set forth in 45 CFR Part 46. The OHRP website is http://www.hhs.gov/ohrp/

9. ***A FEDERAL WIDE ASSURANCE (FWA)*** is an institution's written assurance to OHRP that the institution will abide by ethical principles set forth in the Belmont Report and by the Federal regulations that protect human subjects. The IRP currently operates under an FWA.

G. RESPONSIBILITIES

The IRP's Human Research Protection Program ("HRPP") is made up of NIH ICs, NIH officials, NIH IRBs, researchers and staff who conduct and support research involving human subjects.

1. NIH OFFICIALS RESPONSIBLE FOR OVERSIGHT OF THE HRPP

a. The Deputy Director for Intramural Research (DDIR) is the NIH official responsible overall for the IRP's HRPP. The DDIR, through written delegated authority from the Director, NIH, is the signatory official for the Federal Wide

Assurance, filed with OHRP, and is responsible for oversight of human subjects research in the IRP.

b. The Associate Director for Clinical Research (ADCR) is also the Director of the NIH's clinical center complex, which is made up of the Mark O. Hatfield Clinical Research Center, a 250-bed research hospital, and the Warren Grant Magnuson Clinical Center, which houses outpatient clinics, research laboratories, and research support services. Also, in conjunction with IC leadership, the ADCR ensures implementation of *The Standards.*

c. The Director, Office of Human Subjects Research (OHSR) reports to the DDIR. Through written delegated authority from the DDIR, the OHSR Director coordinates and oversees the IRP's HRPP on a day-to-day basis. The Director is the human protections administrator for the NIH FWA.

2. NIH INSTITUTE OFFICIALS

a. Institute Directors. The Institute Directors have overall responsibility for their Institutes' intramural activities, but generally delegate authority to the Institutes' Scientific or Clinical Directors.

b. Institute Scientific Directors are responsible for the overall direction of and allocation of resources for all the basic and clinical research programs carried out in their Institute's intramural laboratories and branches and in the clinical center research complex.

c. Institute Clinical Directors report to the Institute Directors or Scientific Directors and are responsible specifically for oversight and conduct of the clinical research programs carried out in the Institute's intramural clinical branches. In consultation with the Scientific Directors and IRB Chairs, they nominate members to the Institutes' IRBs and ensure that the IRBs have adequate resources.

3. RESEARCHERS AND STAFF WHO CONDUCT RESEARCH INVOLVING HUMAN SUBJECTS

All members of the NIH scientific and clinical research staff must have knowledge of what constitutes research involving human subjects and comply with the terms of the NIH FWA and 45 CFR Part 46. (Please refer to Section I of this document for the specific educational requirements.) In addition to this basic knowledge, there are additional requirements for the following investigators:

a. Principal Investigator (PI). PIs are responsible for designing, conducting and monitoring protocols, ensuring the protection of human subjects, overseeing the informed consent process and the integrity and analysis of research data,

including prevention of conflicts of interest by all associate investigators on their protocols. PIs assure that protocols are followed and that data are collected promptly and accurately. They are responsible for ensuring that necessary approvals are obtained. There is only one principal investigator for each protocol. PIs must be qualified members of the credentialed CC senior, junior, research or adjunct staff, registered nurses, pharmacologists, psychologists, or other health professionals. Consultants and students may not act as principal investigators.

b. Lead Associate Investigator. Lead Associate Investigators are individuals who have played a leading role in the formulation, writing and implementation of a clinical research protocol under the mentorship of the protocol's principal investigator. A lead associate investigator may be a physician, a dentist, a Ph.D., an RN, a member of the allied health professions, or a trainee.

c. Associate Investigators (AIs). AIs who are staff in the Clinical Center support the conduct of protocols and consist of credentialed members of the medical staff, nurses, pharmacists, nutritionists and others. There may be several AIs on a protocol. Contractors, non-citizens, fellows, students and non-credentialed clinicians also may serve as an AI.

d. Medical Advisor (MAs). When the PI is not a member of the CC junior or senior staff, or when the Clinical Director, IRB or Director CC, consider it warranted, a Medical Advisor must be identified in the protocol. The Medical Advisor must be a member of the CC junior or senior medical staff.

e. Accountable Investigators. Accountable Investigators are tenured or tenure-track investigators or senior clinicians who are responsible and accountable for the scientific quality and expenditure of resources for protocols. In some Institutes, the Accountable Investigator is the Branch Chief or Department Head.

4. INSTITUTE AND CENTER (IC) RESPONSIBILITIES

In accordance with the *The Standards,* each Institute or Center Clinical Director conducting human subjects research in the IRP is responsible for:

a. The development of a central clinical investigations database that maintains data specified to be collected in the clinical study (either intervention or natural history);

b. The establishment of a quality assurance program with infrastructure that ensures that clinical trials are monitored adequately and centrally;

c. The review of protocols involving human subjects to assess scientific quality, the importance of clinical practice and the appropriateness of the study to the IC;

d. The provision of necessary personnel, office space proximal to patient care areas, and accompanying resources to support the clinical research infrastructure; and

e. The appropriate education and training of clinical investigators on their roles and responsibilities.

5. INSTITUTIONAL REVIEW BOARDS (IRBs)

NIH IRBs review and approve all research involving human subjects conducted in the IRP (unless the research is exempt from IRB review, pursuant to 45 CFR 46.101 (b)) in accord with the regulatory mandates to protect subjects' rights and safeguard their welfare. The NIH IRP maintains 14 IRBs, in part because the NIH Institutes and Centers are administratively separate organizations with discrete missions and research portfolios. However, all IRBs follow the requirements of NIH's FWA, the NIH Standard Operating Procedures for IRBs (http://ohsr.od.nih.gov.), the *Clinical Center Medical Administrative Series Policies ("MAS Policies")*, (http://intranet.cc.nih.gov/mec/mas/), and *The Standards,* (http://www.cc.nih.gov/ccc/clinicalresearch/standards1.html).

The 14 NIH Institutional Review Boards are:

- NCI
- NCI Special Studies
- NEI
- NHGRI
- NHLBI
- NIAAA
- NIAID
- NICHD
- NIDA
- NIDDK/NIAMS
- NIDCR
- NIEHS
- NIMH
- NINDS/NIDCD/NIA

The Clinical Center, National Institute of Nursing Research (NINR), National Institute of Biomedical Imaging and Bioengineering (NIBIB), and National Center for Complementary and Alternative Medicine (NCCAM) may rely on

any NIH IRB listed above, depending on the nature of the protocol and the expertise needed for its review.

H. IMPLEMENTATION

1. NIH OFFICE OF HUMAN SUBJECTS RESARCH (OHSR)

The OHSR reports directly to the DDIR. It helps IRP researchers, research staff, IRBs and others understand and comply with the ethical guidelines, regulatory requirements and NIH policy and procedures for research involving human subjects. Specifically, OHSR:

a. Assists various NIH intramural components in administering and managing human subjects research activities so as to promote the rights and welfare of human subjects and the NIH's research mandate.

b. Provides advice on the Federal regulations for the protection of human subjects for the IRP and works with various NIH groups to formulate and develop NIH policies and procedures consistent with these regulations.

c. Plans, organizes and conducts educational activities for NIH intramural personnel about human subject protections, including a mandatory computer-based training program for research staff and a computer-based training program specifically for IRB members.

d. Works closely with the NIH's IRBs to assist them to fulfill their mandate to protect the rights and welfare of human subjects.

e. Assists investigators in identifying and resolving ethical and regulatory issues associated with the design and conduct of their protocols, including studies conducted at non-NIH sites in the U.S. and overseas.

f. Is the sole authority in the IRP for determining which research activities are exempt from the 45 CFR Part 46 regulations.

g. Maintains records and tracks IRB membership, exemptions, and serious unexpected adverse events that may occur on intramural protocols.

h. Maintains a web site containing computerized training programs, forms, information sheets, etc., http://www.nihtraining.com/ohsrsite/.

i. Assists in the conduct of inquiries and/or investigations concerning the conduct of human subjects research in the IRP.

j. Acts as liaison with the DHHS OHRP on matters pertaining to the NIH HRPP.

k. Develops and maintains Standard Operating Procedures (SOPs) for IRBs.

2. IRB PROCEDURES

The 14 NIH IRBs consist of about 200 members. NIH IRBs review four general types of research protocols: (a) clinical trials, (b) screening for prospective research subjects, (c) investigator training protocols, and (d) natural history protocols.

a. Pre-IRB Scientific Review. In accordance with *The Standards,* the Clinical Director and Scientific Director of each IC must ensure that there is a process for reviewing the scientific merit of protocols before they are submitted for review to an NIH IRB.

b. IRB Standard Operating Procedures. In fulfilling the mandate to protect the rights and safeguard the welfare of human research subjects, each NIH IRB operates according to basic procedures set forth in the IRP's SOPs for IRBs. IRBs are permitted to augment these procedures with specific IC requirements if they wish but they are not allowed to omit any of the required procedures. Contact the appropriate IRB for IC-specific SOPs.

c. IRB Composition. Every effort is made to assure diversity of membership and to provide sufficient scientific and ethical expertise for the NIH IRBs to protect the rights and safeguard the welfare of human research subjects. In addition to the minimum Federal regulatory requirements for IRB membership, MAS Policy M-93 (rev) requires that each IRB includes at least one member of the NIH scientific or professional staff not affiliated with the IRB's IC, a biostatistician, and a representative of the Clinical Center Department of Clinical Bioethics. An IRB Chair may also use *ad hoc* consultants to provide special expertise when needed.

d. Appointment of Chairs and Members. IRB Chairs and members are nominated by the Institute Scientific and Clinical Directors in consultation with the IRB Chairs, and appointed by the DDIR for one-to-three year renewable terms.

e. IRB Review of Research. IRBs conduct initial and continuing review (at least yearly) of research protocols. In order to approve research an IRB must determine and document in its minutes that the requirements listed in **Appendix 2** are satisfied. (See *Standard Operating Procedures for NIH Intramural IRBs, OHSR website.)*

f. Conflict of Interest. In accordance with 45 CFR 46.107, no IRB member may participate in an IRB's initial or continuing review of any protocol in which the member has a real or an apparent conflict of interest, except to provide information requested by an IRB.

g. IRB Administration and Costs. Each IRB is staffed by one or more Protocol Coordinators/Administrators. The costs of running and staffing the IRBs and providing space for IRB offices and files are borne by the individual ICs, as specified in *The Standards.*

h. Data and Safety Monitoring. NIH requires that each IC have a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data. Please refer to OHSR Information sheet # 18, OHSR website, http://ohsr.od.nih.gov/ . As explained in that information sheet, this policy was published in the *NIH Guide for Grants and Contracts*, e.g. (1) http://grants.nih.gov/grants/guide/notice-files/not98-084.html; (2) http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html; and (3) http://grants.nih.gov/grants/guide/notice-files/not99-107.html. The NIH policies for data and safety monitoring state:

- PIs are required to create a data and safety-monitoring plan appropriate to each of their protocols.

- IRBs are required to review and approve the plan and determine what kind of safety monitoring process is required (e.g., principal investigator monitoring only, a single independent monitor, or a full data and safety monitoring board {DSMB}). When appropriate, the IC Clinical Director is responsible for appointing an independent monitor or convening a DSMB if an applicable Institute DSMB or independent monitor does not already exist.

- The PI is responsible for providing all required data to the individual monitor or the DSMB, acting upon and informing the IRB of any findings made by the DSMB.

i. Adverse Event Reporting Requirements. In accordance with DHHS and FDA regulations, the NIH IRP has written procedures for ensuring prompt reporting to the IRBs and appropriate NIH officials of any unanticipated problems involving risks to subjects or others, or unexpected serious harm to subjects. Please refer to the OHSR website for NIH guidance on "adverse events," http://ohsr.od.nih.gov/. Consistent with the FDA, the NIH defines a serious adverse event as any untoward medical occurrence that: (a) results in death, (b) is life-threatening, (c) requires (or prolongs) hospitalization, (d) causes persistent or significant disability/incapacity, (e) results in congenital anomalies or birth defects, or (f) is another condition which, in the judgment of the investigator, represents significant hazards.
The OHSR receives reports of all serious, unexpected adverse events and, as warranted, transmits the reports to the OHRP.

j. IRB Performance Evaluation and Monitoring. OHSR staff regularly attend IRB meetings to evaluate IRB operations.

3 THE CLINICAL CENTER COMPLEX

The clinical center complex, consisting of the Warren Grant Magnuson Clinical Center and the Mark O. Hatfield Clinical Research Center, provides inpatient and outpatient hospital facilities for conducting biomedical and behavioral research. The hospital's proximity to the IRP's research laboratories facilitates the rapid translation of research from the bench to the bedside. Each Institute with a clinical research program participates in the usage and cost of the Clinical Center and provides its own infrastructure (laboratories, physical plant, space and personnel (e.g., physicians, nurses, support staff) to sustain its clinical research program.

Some CC programs and departments that particularly contribute to the human subjects protection program include, but are not limited to:

a. The Office of the Deputy Director for Clinical Care is responsible for clinical quality and clinical performance improvement.

b. The Office of Protocol Services (OPS) provides a centralized service for the development, approval, implementation, monitoring and evaluation of protocols. OPS's database tracks all intramural program protocols, except those conducted by NIDA and NIA in Baltimore. OPS services include

accrual reporting to monitor involvement in research by women and minorities, and administratively suspending or terminating protocols whose continuing IRB reviews are not completed and received by OPS by the due date. OPS is also involved in the implementation of *ProtoType*, a secure, web-based clinical protocol writing tool that provides a standardized electronic format for writing and submitting protocols to IRBs. *ProtoTtype* includes electronic links to IRP policies and procedures, https://prototype.cc.nih.gov. In addition *ProtoType* tracks performance of protocols and assists with adverse event reporting, among other features.

c. The Medical Record Department maintains medical records of all subjects registered as patients at the NIH Clinical Center.

d. The Pharmacy Department provides pharmaceutical services and research support to research participants and investigators, including: provision of drug information; development, formulation, distribution and dispensing of drugs; investigational drug information development and control; and assisting investigators with meeting FDA regulatory requirements for filing Investigational New Drug applications. Pharmacy staff members actively conduct and participate in pharmacokinetic studies and various research programs about optimal dosing and appropriate use of investigational and commercially available agents. The Medical Administrative Series policies include guidance for clinical research investigators about the safe management of investigational drugs and other medications used in clinical research in the CC, http://intranet.cc.nih.gov/mec/mas/.

e. The Department of Clinical Bioethics conducts research in bioethics and organizes ethics grand rounds. It also provides consultants to help research subjects, their families, investigators and other CC staff in the resolution of clinical ethical issues. The Department of Clinical Bioethics provides advice, upon request, to investigators in the development of protocols and informed consent documents.

f. The Patient Representative Program promotes effective communication between investigators and research subjects and assures subjects of an unbiased resource for information or assistance about the research in which they are participating.

g. The Nursing and Patient Care Services Department provides nursing services in support of research protocols for all Institutes. Each Institute also employs its own specialized research nurses who participate in and coordinate research protocols.

h. The Patient Recruitment and Public Liaison Office provides information to the public about participation in research being conducted at the Clinical Center.

i. The Clinical Research Volunteer Program provides information to interested persons on the approximately 300 protocols that enroll healthy volunteers. It also ensures that such volunteers are properly registered and, when appropriate, compensated.

j. The Patient Advisory Group, consisting of patient representatives from the ICs using the CC, advises the Director, CC, on patient issues related to care and clinical research.

4. RESEARCH SUBJECTS: RIGHTS AND RESOURCES

In the NIH IRP, the rights, safety and welfare of the subjects who participate in research are paramount. In addition to Federal regulatory protections for research subjects, the Clinical Center undertakes many additional steps to ensure that research subjects are informed and cared for properly.

a. Information.
The Clinical Center web site provides a list of current studies and how to obtain more information about them. Once enrolled, subjects are kept informed in various ways, including the following:

- *The Clinical Center Patient Handbook* is given to all subjects at the time of admission to the hospital as an inpatient or outpatient. Section Two includes the Patient Bill of Rights, and other topics, including confidentiality. As a part of this handbook, the Clinical Center pamphlet *Partners in Research: Volunteer Patients and the Clinical Center* addresses basic questions about participation in clinical research. It includes definitions and descriptions of common clinical research terms such as "randomization," "placebo," and "double-blind." A general discussion of research risks, informed consent, and the role and function of the IRB is also included in this pamphlet.

- Protocol informed consent documents and the process of obtaining informed consent help educate research subjects. Often, copies of the informed consent document are sent to prospective subjects before admission, to familiarize them with protocol requirements.

b. Complaints and Concerns may be addressed in several ways:

- By speaking directly to a PI or AI.

- By speaking to the CC Patient Representative, whose telephone number appears on all consent documents, and/or to nursing staff, social workers or representatives of the CC Spiritual Ministry Department, or OHSR staff.

- By requesting a consultation with a member of the Department of Clinical Bioethics.

- By requesting a consultation with the CC Ethics Committee.

- By withdrawing from participation in research at any time without penalty.

c. Costs: There is no charge for research participation at the CC or for ancillary medical care in the CC related to research protocols for research subjects or healthy volunteers. No patient is denied access to the Clinical Center because of socio-economic status.

d. Compensation: The Principal Investigator and the IRB determine whether compensation is appropriate, and if so the amount of compensation. The CC Clinical Research Volunteer Program (CRVP) registers all research subjects receiving compensation. When NIH employees enroll in research in which they are compensated, they must request annual leave or leave without pay. (See NIH Manual chapter 2300-630-3, "Leave Policy for NIH Employees Participating in NIH Medical Research Studies.")

e. Translation and Interpreting Services. Special efforts are made to ensure that subjects with no or limited proficiency in English receive the same high quality care and information as English-speakers. The CC Social Work Department provides an interpreter service to assist with obtaining informed consent and with promoting subjects' understanding throughout their participation in a study. The NIH policy on informed consent (Medical Administrative Policy 77-2, (http://internal.cc.nih.gov/policies/PDF/M77-2.pdf) includes specific requirements for obtaining informed consent from non-English speaking subjects.

f. Privacy and Confidentiality. Every effort is made to protect the privacy and confidentiality of subjects' medical and research records. Subjects are informed in consent documents of the extent of this protection and their rights under the Federal Privacy Act and any other applicable confidentiality and privacy protections.

g. Vulnerable Subjects. Special attention is given to persons susceptible to coercion or undue influence who have specific needs for protection such as the seriously ill, the mentally ill, children, and cognitively impaired adults. (See Appendix 1, MAS 87-4 [rev], "Consent Process in Research Involving Impaired Human Subjects," and MAS 92-5 [rev], "Research Involving Children and Children's Assent to Research.") As appropriate, NIH IRBs consider additional protections for vulnerable subjects, such as requiring bioethics consultations, requiring consent monitors, or requiring frequent IRB review of a protocol.

h. Special Facilities. The Children's Inn, located close to the Clinical Center on the NIH campus, is a private, non-profit residence with the purpose of keeping children together with their families while they are in Bethesda to participate in research studies. The Edmond J. Safra Family Lodge, a similar facility for adults, has 34 guest rooms and serves as a retreat and sanctuary for families and caregivers of NIH Clinical Center subjects participating in investigational and clinical trials.

5. PRINCIPAL NIH COMMITTEES INVOLVED IN THE FORMATION OF POLICY DEVELOPMENT FOR THE PROTECTION OF HUMAN SUBJECTS

a. The Medical Executive Committee (MEC) is advisory to the Director, CC, and is comprised of all the IC Clinical Directors and senior members of some CC medical departments, services and branches (e.g., critical care medicine, pediatrics, surgery). The MEC meets twice monthly to provide advice and guidance to the Director, CC and the NIH community about issues that relate directly to clinical care and research support within the IRP. It is chaired by a Clinical Director elected by the membership. It ensures that NIH intramural clinical research investigators are afforded the resources necessary to support their research, and oversees the provision of safe care and protection to research participants. The MEC approves the Medical Administrative Series Policies (MAS), which govern research and clinical care in the clinical center complex. The MEC also monitors compliance with *The Standards.*

b. The Human Subjects Research Advisory Committee (HSRAC) meets every other month. Chaired by the DDIR, it advises him/her about the conduct of human subjects research in the NIH IRP. It is a forum for the dissemination of new information, policies and procedures, including those of the OHRP and the FDA. Membership consists of the 14 IRB Chairs, the Director, CC, the Chief of the CC Department

of Clinical Bioethics, the Director, OHSR (Executive Secretary), a representative of the NIH Fellows Committee, a member of the NIH Radiation Safety Committee, a representative of the Protocol Coordinators/Administrators, and a lay member. Protocol administrative staff and other interested CC staff attend as guests.

c. The Trans-NIH Bioethics Advisory Committee (TNBC) coordinates policy development among the Institutes and the Office of the Director (OD), NIH, in the areas of ethical, legal and social implications of NIH-funded research, including the research of the IRP. The Committee meets monthly, or as needed, and is chaired by the Associate Director for Science Policy, OD. It is composed of senior staff members designated by the IC Directors. Relevant OD offices, including the OHSR, are also represented.

6. OTHER NIH COMMITTEES INVOLVED IN SAFETY AND MONITORING

In addition to IRBs, there are several specialized NIH committees involved in ensuring the safety of IRP research subjects and NIH staff during the conduct of research protocols.

a. The Radiation Safety Committee (RSC) is responsible to the Director, NIH for oversight of the NIH Radiation Safety Program to ensure the safe use of radioactive materials and all sources of ionizing radiation throughout NIH and those NIH-occupied buildings included in the NIH Radiation Safety Program. The RSC is responsible for formulating policy with regard to radiation protection matters in the intramural program that involve NIH employees and members of the general public, routine clinical and research programs, and protection of the environment to ensure compliance with Federal regulations, including those of the U.S. Nuclear Regulatory Commission.

b. The Radioactive Drug Research Committee (RDRC) functions as a subcommittee of the RSC and is mandated by the Food and Drug Administration (FDA) Regulations, 21 CFR Part 361.1, "Radioactive Drugs for Certain Research Uses," to review and approve the use of radioactive drugs for research purposes in humans for which an approved New Drug Application (NDA) or an approved Investigational New Drug Application (INDA) does not exist.

c. The Office of Biological Activities (OBA), and the Recombinant DNA Advisory Committee. OBA is responsible for oversight and policy development regarding the scientific, safety, and ethical issues

associated with basic and clinical recombinant NIH research. This role includes implementation of the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*), which articulate principles of containment and biosafety review for this type of research. A key element of this system of oversight is the NIH Recombinant DNA Advisory Committee (RAC), which reviews human gene transfer protocols and makes recommendations to PIs and others on improving the science, safety and ethics of their trials. The RAC also advises the NIH on scientific, safety, and policy matters related to the use of recombinant DNA in research generally, including needed modifications of the *NIH Guidelines*. Local review of recombinant DNA research is carried out by Institutional Biosafety Committees (IBC), which must register with OBA to ensure that they are properly constituted. Most intramural trials involving human gene transfer need to be registered with OBA and reviewed by the RAC. Further, basic and clinical research involving recombinant DNA should be registered, and in many cases reviewed, by the NIH IBC. More information on the RAC and IBCs can be found at: http://www4.od.nih.gov/oba/Rdna.htm.

d. The Institutional Biosafety Committee (IBC), Office of Research Services: This committee, created pursuant to the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*; http://www4.od.nih.gov/oba/rac/guidelines/guidelines), reviews basic and clinical research involving recombinant DNA, including human gene transfer, to ensure that proper containment and biosafety practices are employed. When reviewing human gene transfer protocols, the IBC also oversees compliance with Appendix M of the *NIH Guidelines*, which details points to consider in the design of human gene transfer protocols and their submission to the NIH Office of Biotechnology Activities.

7. COLLABORATIVE AND SPONSORED RESEARCH

a. Definition of collaboration. In the IRP, collaboration exists if the NIH PI expects "something in return" as a result of having participated in a research activity. "Something in return" could include data, authorship on a publication, samples, or even patent rights. The NIH views authorship as *prima facie* evidence of collaboration. Collaborative activities may include but are not limited to: the collection of specimens, visits to institutions to perform research activities or clinical work, exchange of information containing personal identifiers, preliminary data-collection activities involving human subjects, and substantive

intellectual contributions to research techniques, protocol design, or interpretation of data. Even remote participation--such as supplying important reagents, performing tests, or analyzing data--may constitute collaboration. Investigators should contact their IRB Chair or the OHSR for guidance in cases where it is unclear whether or not collaboration exists.

b. Participation in off-site protocols. Some intramural protocols are conducted at non-NIH locations, or intramural investigators participate in protocols at non-NIH locations in the United States and abroad in collaboration with investigators from other institutions. Generally, such collaborations may take place only with institutions that have OHRP-approved Federal Wide Assurances. NIH IRP IRBs review and approve collaborative protocols and receive written confirmation of completed initial and continuing review approvals by IRBs at the collaborating sites. OHSR provides guidance to IRP researchers about appropriate collaborative arrangements.

8. RESEARCH CONDUCTED OR SUPPORTED BY OTHER ORGANIZATIONS OR INSTITUTIONS

NIH Institutes may participate as performance sites in research conducted or supported by, or in collaboration with others, such as other federal agencies, non-profit foundations, academic centers and pharmaceutical companies. The NIH IRP conducts research with external collaborators through Memoranda of Understanding (MOUs), Cooperative Research and Development Agreements (CRADAs), Material Transfer Agreements (MTAs) and Inter-institutional Agreements (IIAs). NIH IRBs review all such protocols in the same way as they do other intramural protocols and place whatever requirements on the protocol and consent procedures that they determine necessary to protect human subjects. If the collaborator does not agree to such alterations, the study is not approved for implementation in the NIH IRP.

9. CONFLICT OF INTEREST REGULATIONS, POLICIES AND GUIDANCE

a. NIH and the U.S. Department of Health and Human Services have developed regulations and resources to help ensure transparency regarding outside activities and proactive management of conflicts of interests. These regulations apply to all federal NIH employees, except Special Government Employees. The regulations and related resources can be found at the following website: http://www.nih.gov/about/ethics_COI.htm

b. The NIH IRP has implemented a "Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH," for all NIH intramural scientists. That guide can be found on the OHSR website: http://ohsr.od.nih.gov/New/mpafwa_docs.html

c. IRB members are expected to disclose any financial or other conflict of interest that may prevent them from providing objective review of any pertinent protocol. No IRB member may participate in the IRB's initial, continuing or amendment review of any protocol in which the member has a real or an apparent conflict of interest, except to provide information requested by the IRB, pursuant to 45 CFR 46.107(e). Consequently, researchers who are IRB members are not permitted to review or approve any protocols in which they are involved.

I. EDUCATION

Clinical research training programs for scientists and other protocol participants in the Intramural Program are overseen by the Office of the Clinical Research Training, housed in the Clinical Center. Monitoring for investigators' compliance with training requirements is provided by the CC Office of Protocol Services. Monitoring of training for IRB members is done by OHSR.

1. INVESTIGATORS

a. Requirements

- Completion of the OHSR computer based training (CBT) for researchers and research staff, titled, "Protecting Human Subjects," is required of all researchers newly-employed by the NIH, contract staff who work within NIH intramural laboratories, and any other NIH staff who conduct or support clinical research (See NIH Manual Chapter 2300-935, Appendix I). The course can be accessed through the OHSR website, http://ohsr.od.nih.gov.

- PIs on all Clinical Center protocols must complete the Clinical Center's *Clinical Research Training Course* and pass a multiple-choice examination. This course is available on the CC's web site and was developed by staff from the CC, the NIH Institutes, the OHSR and the FDA. No new protocols are approved, nor are existing protocols renewed, without certification that PIs have completed these requirements. (See NIH Manual Chapter 2300-935, Appendix I.)

b. Optional educational opportunities for investigators and research staff

- *Ethical and Regulatory Aspects of Human Subjects Research*. PIs and AIs are strongly encouraged to complete the seven-session *Ethical and Regulatory Aspects of Human Subjects Research* course conducted annually by the CC Clinical Bioethics Department.

- *Introduction to the Principles and Practice of Clinical Research.* This annual course teaches researchers how to develop a well constructed and well-designed clinical research protocol. The course covers epidemiological methods and focuses on study design and development, protocol preparation, patient monitoring, quality assurance and FDA issues. It also includes data management strategies and legal and ethical issues, including the protection of human subjects.

- Master's Degree in Clinical Research. The NIH Clinical Center, Duke University and the University of Pittsburgh collaborate to offer two separate programs with NIH. NIH participants complete coursework primarily through videoconferences with faculty at Duke and the University of Pittsburgh. A Master of Health Sciences in Clinical Research is awarded for successful completion of the program.

- *Principles of Clinical Pharmacology.* This annual CC program provides detailed information to researchers about the clinical aspects of drug development and use. It also includes a review of pharmacokinetics, drug metabolism and transport, assessment of drug effects, drug therapy in special populations and contemporary drug development.

- CC Clinical Grand Rounds are held every week. Every quarter, a session is devoted to Ethics Grand Rounds, which deals with ethical issues in clinical research or medical practice. Continuing medical education credit is given for attendance at Rounds under NIH's accredited ACCME program.

- An NIH Certificate in Clinical Research is available for physicians, dentists and allied health professionals fully engaged in or intending to become engaged in clinical translational investigation. Individuals who complete the mandatory components of the program are awarded

a certificate by the NIH Clinical Center. The requirements of the program are set forth in the following NIH intranet website: http://intranet.cc.nih.gov/clinicalresearchtraining/curriculumcert.shtml

2 IRB CHAIRS, MEMBERS AND STAFF

a. Requirements
IRB Chairs and members are required to certify completion of the *NIH OHSR Computer Based Training (CBT) for Researchers and Research Staff* and the *OHSR CBT for NIH IRB Members*. Before starting service on an IRB, they must attend an individual orientation session with an OHSR staff member at which they discuss their responsibilities and are given copies of the relevant regulatory information and other documents pertaining to the conduct of human subjects research at the NIH.

b. Other educational opportunities for IRB chairs, members and staff

Research staff and Chairs and members of IRBs are encouraged to participate in various continuing education activities, provided by OHSR, the CC and others, such as NIH courses, seminars, ethical grand rounds, briefings, etc; to attend national and regional meetings sponsored by organizations such as the Applied Research Ethics National Association (ARENA) and Public Responsibility in Medicine and Research (PRIM&R), and to attend educational retreats or other activities sponsored by an individual NIH IRB, Institute or Center.

J. RECORDS RETENTION AND DISPOSAL

1. Pursuant to 45 CFR 46.115(a) and 21 CFR 56.115(a) the NIH, IRB administrative offices prepare and maintain certain IRB records, including copies of research proposals, scientific evaluations, consent documents, records of IRB actions, minutes of IRB meetings, records of continuing review activities, a list of IRB members, a written summary of the discussion of controverted issues and their resolutions, written procedures for IRBs, and statements of significant new findings provided to subjects. 45 CFR 46.115(b) and 21 CFR 56.115(b) state that records required by the regulations should be retained for at least three years after completion of the research.

2. All records pertaining to this Manual Chapter (e-mail and non-e-mail) must be retained and disposed of under the authority of NIH Manual 1743, Keeping and Destroying Records, Appendix 1, NIH Records Control Schedule, Items: 1100-H-2, committee records, and 3000-G-2-b,

biomedical research protocol records related to human subjects (CC Protocol File).

3. NIH e-mail messages (messages, including attachments, that are created on NIH computer systems or transmitted over NIH networks) that are evidence of the activities of the agency or have informational value are considered Federal records. These records must be maintained in accordance with current NIH Records Management guidelines. The IC Records Officer may be contacted for additional information.

4. All e-mail messages are considered Government property, and, if requested for a legitimate Government purpose, must be provided to the requester. Employees' supervisors, NIH staff conducting official reviews or investigations, and the Office of Inspector General may request access to or copies of the e-mail messages. E-mail messages must also be provided to Congressional oversight committees if requested and are subject to Freedom of Information Act requests. Since most e-mail systems have back-up files that are retained for significant periods of time, e-mail messages and attachments are likely to be retrievable from a back-up file after they have been deleted from an individual's computer. The back-up files are subject to the same requests as the original messages.

K. MANAGEMENT CONTROLS

The purpose of this Manual is to establish responsibility for the protection of human subjects within the NIH IRP.

1. Offices Responsible for Reviewing Management Controls Relative to this Manual: Office of Human Subjects Research and the Office of Intramural Research.

2. Frequency of Review: Ongoing; at least annually.

3. Method of Review: Alternative Review. The IC Directors or Scientific Directors participate in the Annual Intramural Self Assessment of Management Controls, through completion of a set of comprehensive checklists of questions. The Office of Intramural Research manages this process. Also, the NIH HRPP is subject to regulatory oversight by the FDA and the OHRP.

4. Review reports are sent to the Deputy Director for Intramural Research (DDIR).

APPENDIX 1- REFERENCES

ETHICAL REQUIREMENTS PERTAINING TO HUMAN SUBJECTS

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979, http://www.nihtraining.com/ohsrsite/guidelines/guidelines.html

FEDERAL STATUTES

Food, Drug and Cosmetic Act of 1938 (as amended)
New Drug Amendments of 1962
Radiation Control for Public Health and Safety Act of 1968
National Research Act of 1974
Medical Device Amendments of 1976
Safe Medical Devices Act of 1990
Device Amendments of 1992
FDA Modernization Act of 1997
Freedom of Information Act of 1966
The Privacy Act of 1974

Federal conflict of interest statutes are found on the website of the NIH Ethics Program at http://ethics.od.nih.gov/LawRegs.htm

FEDERAL REGULATIONS

Title 45 Code of Federal Regulations, Part 46, Protection of Human Subjects, http://www.nihtraining.com/ohsrsite/guidelines/guidelines.html

Title 21: Foods and Drugs
http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200221

Title 21, Part 11,-"Electronic Records: Electronic Signatures"
Title 21, Part 50, "Protection of Human Subjects"
Title 21, Part 54, "Financial Disclosures by Clinical Investigators"
Title 21, Part 56, "Institutional Review Boards"
Title 21, Part 312, "Investigational New Drug Application"
Title 21, Part 361.1, "Radioactive Drugs for Certain Research Uses"
Title 21, Part 812, "Investigational Device Exemption"

NIH Guidelines for Recombinant DNA and Gene Transfer
http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

Regulations promulgated by the Office of Government Ethics are found on the website of the NIH Ethics Program, http://ethics.od.nih.gov/LawRegs.htm Supplemental Standards of Ethical Conduct and Financial Disclosure Requirements for Employees of the Department of Health and Human Services are found on the website of the NIH Ethics Program, http://www.nih.gov/about/ethics_COI.htm

NIH POLICIES

NIH policies pertaining to conflict of interest are found on the website of the NIH Ethics Program, http://ethics.od.nih.gov/LawRegs.htm

The NIH Intramural "Guide to Preventing Conflicts of Interest in Human Subjects Research at NIH," is found on the OHSR website at http://ohsr.od.nih.gov/New/mpafwa_docs.html

NIH Policy for Data and Safety Monitoring, NIH Guide, June 10, 1998 and June 5, 2000; a summary of the NIH policy and NIH Guide citations are found in OHSR Information sheet 18, http://www.nihtraining.com/ohsrsite/info/sheet18.html

NIH Policy for the Inclusion of Women and Children as Subjects of Clinical Research, NIH Guide, August, 2000, amended October, 2001; a summary of the NIH policy and citations are found in OHSR Information Sheet 11, http://www.nihtraining.com/ohsrsite/info/sheet11.html

NIH Policy for the Inclusion of Children as Subjects of Clinical Research, NIH Guide, March 6, 1998, is set forth on the NIH Extramural website, http://grants2.nih.gov/grants/funding/children/children.htm

NIH Policy Manual 2300-735-1, "Avoiding Conflicts of Interest." and other NIH ethics policies are found on the website of the NIH Ethics program, http://ethics.od.nih.gov/LawRegs.htm

Medical Administrative Series Policies of the NIH Clinical Center, http://intranet.cc.nih.gov/mec/mas/

M01-2 (rev.), "Procurement and Use of Human Biological Materials for Research," (4/22/2003)
M03-5, "CC Medical Staff Bylaws," (11/06/2003)
M77-2 (rev.), "Informed Consent, "(3/7/2003)
M80-3 (rev.), "Use of Investigational or New Drugs in Patient Care," (7/17/2003)
M81-2 (rev.), "Disclosure of Patient Information to Third Parties, "(11/4/2003)

M87-4 (rev.), "Consent Process In Research Involving Impaired Subjects" (9/16/2003)
M89-1 (rev.), "HIV Testing" (9/19/2003)
M92-5 (rev.), "Research Involving Children and Children's Assent to Research," (11/1/2002)
M92-7 (rev.), "Advance Directives," (9/2/2003)
M93-1 (rev.),"Research Involving Human Subjects At the Clinical Center: Structure and Process," (9/16/2003)
M95-9 (rev.), "Guidelines for Blood Drawn for Research Purposes in the Clinical Center," (9/5/2003)
M97-2 (rev.), "Guidelines for Writing Research Protocols," (9/16/2003)

Standard Operating Procedures for NIH Intramural IRBs, March 2003, Office of Human Subjects Research website, http://www.nihtraining.com/ohsrsite/New/mpafwa_docs.html

The Standards for Clinical Research Within the NIH Intramural Program, January 2000, Clinical Center Medical Executive Committee, Clinical Center website http://www.cc.nih.gov/ccc/clinicalresearch/standards1.html

STANDARDS AND GUIDELINES

Guidelines for the Conduct of Research In the Intramural Research, 1994, Intramural Research Program, NIH, NIH Intramural Program website, *http://www.nih.gov/campus/irnews/guidelines.htm*

International Conference on Harmonisation (ICH) Guidelines, "Good Clinical Practice: Consolidated Guidelines," http://www.ich.org/

Protomechanics, A Guide to Preparing and Conducting a Clinical Research Study, NIH Clinical Center, http://clinicalcenter.nih.gov/ccc/protomechanics/

ProtoType, a web-based protocol-writing and adverse-event reporting system, http://prototype.cc.nih.gov

U.S. Food and Drug Administration, "Guidance and Information Sheets on Good Clinical Practice in FDA-Regulated Clinical Trials," http://www.fda.gov/oc/gcp/guidance.html

HRPP Manual Chapter --Appendix 2

IRB PROTOCOL REVIEW STANDARDS

The following list of issues must be addressed by NIH IRBs each time that a protocol is reviewed. This list meets minimal federal regulatory requirements and NIH policy requirements. Under each issue are suggested questions for the IRB members to discuss while addressing these points. The IRB minutes must contain documentation that these issues have been addressed by the IRB.

1. The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk.

SUGGESTED QUESTIONS

(a) Is the hypothesis clear? Is it clearly stated?
(b) Is the study design appropriate to prove the hypothesis?
(c) Will the research contribute to generalizable knowledge and is it worth exposing subjects to risk?

2. 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.

SUGGESTED QUESTIONS

(a) What does the IRB consider the level of risk to be? (See risk assessment guide below.)
(b) What does the PI consider the level of risk/discomfort/inconvenience to be?
(c) Is there prospect of direct benefit to subjects? (See benefit assessment guide below.)

3. Subject selection is equitable.

SUGGESTED QUESTIONS

(a) Who is to be enrolled? Men? Women? Ethnic minorities? Children (rationale for inclusion/exclusion addressed)? Seriously-ill persons? Healthy volunteers?
(b) Are these subjects appropriate for the protocol?

4. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence.

SUGGESTED QUESTION

(a) Are appropriate protections in place for vulnerable subjects, e.g., pregnant women, fetuses, socially- or economically-disadvantaged, decisionally-impaired?

5. Informed consent is obtained from research subjects or their legally authorized representative(s).

SUGGESTED QUESTIONS

(a) Does the informed consent document include the eight required elements?
(b) Is the consent document understandable to subjects?
(c) Who will obtain informed consent (PI, nurse, other?) & in what setting?
(d) If appropriate, is there a children's assent?
(e) Is the IRB requested to waive or alter any informed consent requirement?

6. Subject safety is maximized.

SUGGESTED QUESTIONS

(a) Does the research design minimize risks to subjects?
(b) Would use of a data & safety monitoring board or other research oversight process enhance subject safety?

7. Subject privacy & confidentiality are maximized.

SUGGESTED QUESTIONS

(a) Will personally-identifiable research data be protected to the extent possible from access or use?
(b) Are any special privacy & confidentiality issues properly addressed, e.g., use of genetic information?

Additional considerations

1. Ionizing radiation.
(a) If ionizing radiation is used in this protocol is it medically indicated or for research use only?

2. Collaborative research.
(a) Is this domestic/international collaborative research? If so, are FWAs or other assurances required for the sites involved? Is there a CRADA?

3. FDA-regulated research
(a) Is an IND or IDE involved in this protocol?

Risk/Benefit Assessment

RISK

Regulatory definition of minimal risk: 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 (45 CFR 46.102(h)(i)).

Check appropriate risk category:

1. _____The research involves no more than minimal risk to subjects.
2. _____The research involves more than minimal risk to subjects.

    ____The risk(s) represent(s) a minor increase over minimal risk, **or**

    ____The risk(s) represent(s) more than a minor increase over minimal risk.

BENEFIT

Definition: A research benefit is considered to be something of health-related, psychosocial, or other value to an individual research subject, or something that will contribute to the acquisition of generalizable knowledge. Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

Check appropriate benefit category(ies):

1. _____no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition (mainly for patient subjects);

2. ____no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study (mainly for healthy volunteers); or

3. ____the research involves the prospect of direct benefit to individual subjects.