Orientation Information

for Members

of Institutional

Review Boards

at the NIH

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Introduction

The NIH Intramural Research Program (IRP) has a long history of conducting innovative and challenging human subject research. Focused primarily at the NIH's Warren Grant Magnuson Clinical Center in Bethesda, Maryland, this research endeavor has led to many improvements in the nation's health. Other IRP sites include the National Institute on Drug Abuse in Baltimore, Maryland and the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina.

Human subject research conducted at the NIH must meet high ethical and scientific standards. It must be designed, reviewed, approved and implemented in accord with accepted ethical principles, the US Department of Health and Human Services (45 CFR 46) and US Food and Drug Administration (21 CFR 50 and 56) regulations for the protection of human subjects.

The NIH IRP has created a Human Subject Protection Program (HRPP) designed to ensure that all aspects of human subject research function in concert to promote the rights and welfare of our research subjects. The HRPP

is made up of NIH officials including Institute/Center (IC) Scientific and Clinical Directors, clinical investigators, and the staff and resources of the Clinical Center. The NIH Deputy Director for Intramural Research (DDIR) directs the HRPP and the NIH Office of Human Subjects Research (OHSR) oversees its implementation on a day-to-day basis. OHSR is the main IRP office for information about and guidance on the protection of human research subjects. OHSR is located in Building 10, Room 1C116 and may be contacted at 301-402-3444. Its website is http://ohsr.od.nih.gov/.

The centerpiece of the NIH's HRPP is the Institutional Review Board (IRB) whose mandate is to protect the rights and safeguard the welfare of research subjects. Currently, there are fourteen IRBs at the NIH, each of which is NIH Institute-based and administratively supported. All of the IRBs follow OHSR-issued standard operating procedures and are accountable to the NIH DDIR.

The Institutional Review Board

An IRB is a committee with federal regulatory authority to review and approve research involving human subjects. An IRB is composed of a diverse group of men and women with expertise in science, ethics, and other non-scientific areas. This diversity is important as it fosters a comprehensive approach to protecting the rights and safeguarding the welfare of subjects. In addition to their individual skills, experience and perspectives, members are recruited to serve on an IRB based on their independence, professional integrity and willingness to perform a public service. In particular, the NIH highly values service on its IRBs of non-scientific and non-NIH members.

Appointment to the IRB

The DDIR appoints members to serve on an IRB based on nominations from Institute Scientific and Clinical Directors. Members are appointed for one-to-three year renewable terms. Members receive a letter of appointment from the DDIR. IRB Chairs are appointed to their position by the DDIR based on recommendations from Clinical and Scientific Directors.

IRB Member Education

Members bring a wide array of experiences and backgrounds to their IRB service. Being an effective IRB member requires particular knowledge, skills and abilities beyond an intuitive sense of how to protect human research subjects. Therefore, new members are required to complete the OHSR computer-based training program (CBT) for IRB members found at http://ohsr.od.nih.gov (click on "Computer-Based Training" and then on "IRB Members"). This CBT gives an overview of the ethical foundations, regulatory requirements and NIH review requirements for research involving human subjects. Also, before their first meeting, new members are required to meet individually with OHSR staff for an orientation session.

IRB members should familiarize themselves with *The Belmont Report – Ethical Principles and Guidelines for the Protection of Human Subjects* (See Appendix 1). These ethical principles guide the design, review and conduct of research involving people.

Additional education and information resources for IRB members, including *The Belmont Report*, may be found on the OHSR website at http://ohsr.od.nih.gov/.

Conflict of Interest

IRB members must recognize and address real or apparent conflicts of interest associated with their service on the Board. A real or apparent conflict of interest exists when a Board member has certain relationships to research protocols that the Board reviews. Such relationships include the direct conduct of the research protocol, the provision of resources or support for its conduct, or its approval and oversight elsewhere within NIH. Infrequently, members may have a financial conflict of interest with a research protocol under consideration by the IRB. In all cases IRB members must disclose real or apparent conflict of interest to the Board.

No IRB member may participate in the IRB's initial or continuing review of research in which the member has a conflicting interest, except to provide information requested by the IRB.

IRB Meetings

The IRB Chair determines the meeting agenda and conducts the meeting consistent with Roberts Rules of Order.

All of the NIH IRBs function administratively in accord with NIH IRB Standard Operating Procedures (SOPs). These SOPs (available from the IRB) serve as detailed guidance for IRB members, Chairs and IRB administrative staff.

Members receive IRB meeting agendas and review materials before the meeting. It is important that members prepare for meetings and actively participate in Board discussions. Each member's view is important to the IRB's collective decision-making process. Members are expected to attend at least 75% of IRB meetings per year.

Most NIH IRBs meet once or twice a month. The IRB conducts its business at a convened meeting at which a majority of the voting members, including at least one of its non-scientist members, are present. IRB determinations (e.g., approval, disapproval, approval with stipulations, table) require a simple majority vote of the members present.

In general, IRB meetings are open to the public. Meetings are closed when IRB votes are taken and when the Chair determines that a topic of a confidential or proprietary nature will be discussed.

Research Protocols

Protocols are designed and written by Principal Investigators (PIs). A research protocol is a written description of research which follows a structured format and includes discussion of the human subject protections issues. Also, the protocol contains a written informed consent document. Consent documents provide prospective subjects with information they need, including that required by federal regulations, to make an informed decision about whether or not to participate.

NIH requires that before any protocol is submitted to an NIH IRB, it receives pre-IRB scientific review and approval. This is to ensure that the proposed research is scientifically sound and consistent with NIH research objectives. Institutes are given flexibility on how they perform pre-IRB scientific review. Usually the results are available to the IRB when it reviews the protocol.

The full NIH HRPP protocol review process is shown in Appendix 2.

IRB Review of Research

IRBs conduct initial and continuing reviews of research protocols. Appendix 3 provides the review standards followed by the IRB in consideration of new research protocols. The IRB uses the review standards to structure and streamline its discussion of the protocol, and to assure that all regulatory requirements are met in its review and approval of human subject research.

For the initial review of research, the IRB also requires a succinct oral presentation by the Principal Investigator addressing each of the review standards. Such presentations focus the attention of the IRB and the Principal Investigator on the important human subject protection issues required for IRB approval.

In exercising its authority, the IRB may approve, disapprove or table research protocols. Often, IRBs approve research protocols with required changes called stipulations. If an IRB votes to disapprove a particular research protocol, NIH officials cannot approve that research. (However, research which is approved by an IRB must also be approved by NIH officials.)

By federal regulation, the IRB must review and approve previously approved research at least annually. For its continuing review, the IRB uses the same review standards as for an initial review (Appendix 3). The IRB may request information from the PI earlier than one year if it determines that the research presents significant physical, social or psychological risks to subjects. This continuing review of research by the IRB is as important as its initial review. It must be comprehensive in order to ensure that ongoing research includes the appropriate protection of human subjects. During their continuing reviews of protocols, IRBs often require changes in the protocol or informed consent documents.

The IRB may modify, suspend or terminate approval of research that has been associated with serious harm to subjects or is not being conducted in accord with Federal regulations or the IRB's decisions, stipulations and requirements.

IRB Records

Federal regulations and NIH policy require that IRBs maintain adequate documentation of their activities. This includes copies of research reviewed by the IRB and its correspondence with investigators.

In particular, the IRB must maintain minutes of its meetings. IRB minutes must record member attendance (by name) 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 controverted issues and their resolution. The minutes are expected to include a brief discussion of each of the review standards in Appendix 3. Other than attendance, IRB minutes do not normally reference IRB members by name.

IRB meeting minutes are available to the public in accord with the Federal Freedom of Information Act (FOIA).

Summary

Our society acknowledges that gaining knowledge through research involving people is acceptable as long as the research is consistent with ethical principles and regulatory requirements. The NIH views its IRBs as a critical part of its human research protection program. Service on an IRB is rewarding, challenging and an important contribution to the NIH.

Appendix 1
The Ethical Principles of *The Belmont Report*

The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects -- was published in 1979 and provides the philosophical underpinnings for the current laws governing human subjects research. *The Belmont Report* establishes three fundamental ethical principles that are relevant to all research involving human subjects: Respect for Persons, Beneficence, and Justice. Although other important principles sometimes apply to research, these three provide a comprehensive framework for ethical decision-making in research involving human subjects.

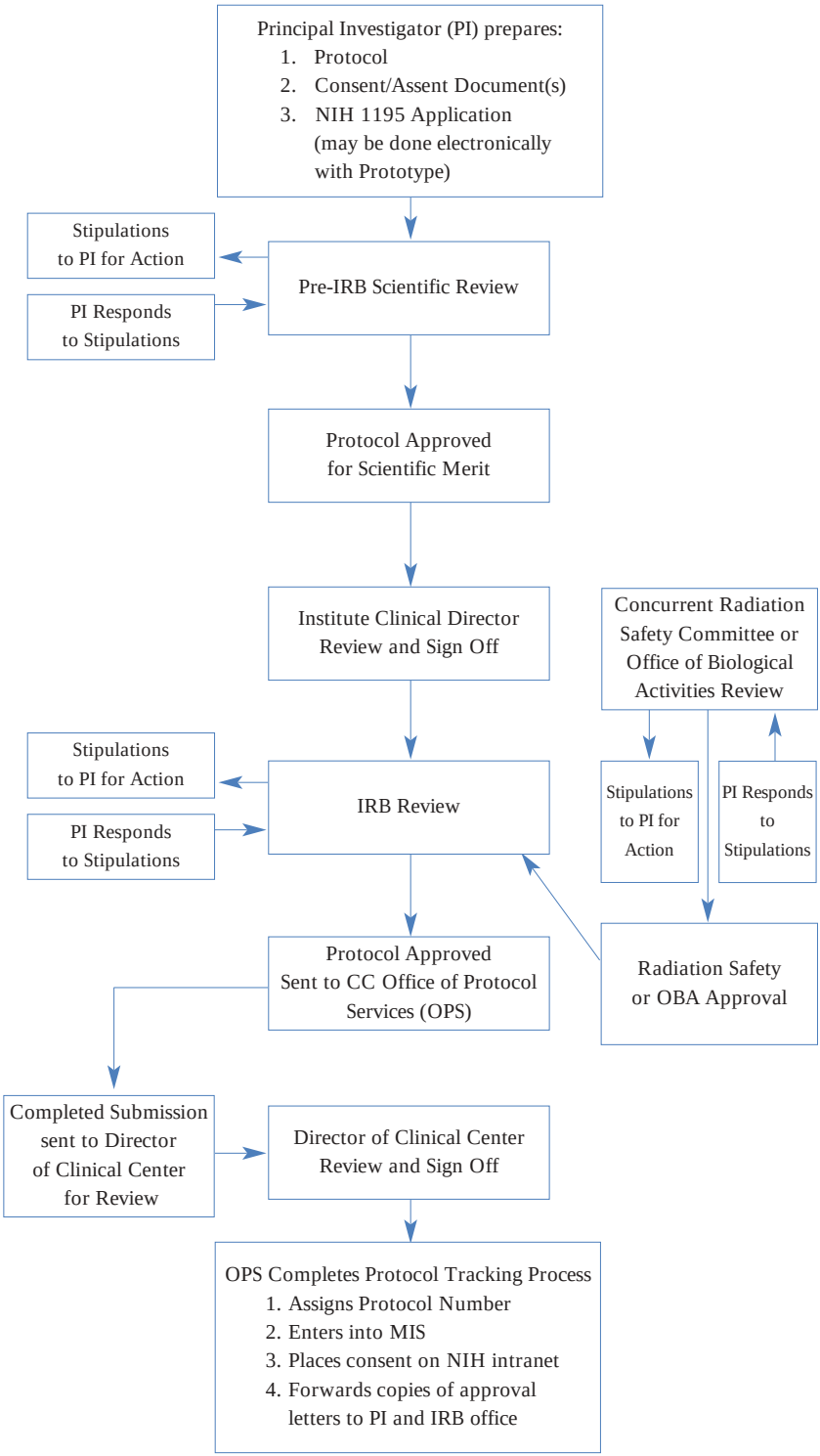
1. The principle of Respect for Persons acknowledges the dignity and autonomy of individuals, and requires that people with diminished autonomy be provided special protection. This principle requires that subjects give informed consent to participation in research. Because of their potential vulnerability, certain subject populations are provided with additional protections. These include children, prisoners, the mentally disabled, and people with severe illnesses.

2. The principle of Beneficence requires us to protect individuals by maximizing anticipated benefits and minimizing possible harms. Therefore, we must examine carefully the design of the study and its risks and benefits including, in some cases, identifying alternative ways of obtaining the benefits sought from the research. Research risks must be reasonable in relation to the expected benefits, if any, to the subjects and the importance of the knowledge that may be expected to result.

3. The principle of Justice requires that we treat subjects fairly. For example, subjects should be carefully and equitably chosen to insure that certain individuals or classes of individuals -- such as prisoners, elderly people, or financially impoverished people -- are not systematically selected or excluded, unless there are scientifically or ethically valid reasons for doing so. Also, unless there is careful justification for an exception, research should not involve persons from groups that are unlikely to benefit from subsequent applications of the research.

Each of these principles carries strong moral force and difficult ethical dilemmas arise when they conflict. A careful and thoughtful application of the principles of *The Belmont Report* by IRB members will not always achieve clear resolution of ethical problems. However, it is important to understand and apply the principles, because doing so helps to assure that people who agree to be experimental subjects will be treated in a respectful and ethical manner.

Appendix 2
Protocol Approval Process in the Intramural Program at the NIH



Appendix 3
IRB Protocol Review Standards
Minimal regulatory requirements for IRB review, discussion and documentation in the meeting minutes

Regulatory review requirement (see 45 CFR 46.111)
1. The proposed research design is scientifically sound & will not unnecessarily expose 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.
3. Subject selection is equitable.
4. Additional safeguards required for subjects likely to be vulnerable to coercion or undue influence.
5. Informed consent is obtained from research subjects or their legally authorized representative(s).
6. Risks to subjects are minimized.
7. Subject privacy & confidentiality are maximized.

Additional considerations
1. Ionizing radiation.
2. Collaborative research.
3. FDA-regulated research
4. Other

Suggested questions for IRB discussion

(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?

(a) What does the IRB consider the level of risk to be?
(See risk assessment guide on back of form.)
(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 on back of form.)

(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?

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

(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?

(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?

(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?

If ionizing radiation is used in this protocol is it medically indicated or for research use only?

Is this domestic/international collaborative research? Are assurances in place? Is there a CRADA?

Is an IND or IDE involved in this protocol?

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(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) represents a minor increase over minimal risk, **or**

   _____ The risk(s) represents 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:

1. _____ The research involves no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition.

2. _____ The research involves the prospect of direct benefit to individual subjects.

Where to Go For Help and Information

- To obtain a copy of your IRB's Standard Operating Procedures,
  - ask your IRB's Protocol Coordinator.

- For general educational materials or other information about the NIH's human research protection program,
  - go to OHSR's web site at http://ohsr.od.nih.gov/,
  - call OHSR at 301-402-3444, or
  - ask your IRB's Chair or Protocol Coordinator.

- Other offices located on the NIH campus with interest and expertise in the ethical and regulatory aspects of human subject research:
  - The Clinical Center Department of Bioethics (301-496-2429)

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