Guidelines

for the

Conduct of

Research Involving Human Subjects

at the
National Institutes
of Health

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In this brochure you will find background and guidelines on the ethical and regulatory aspects of research on fellow human beings. The NIH has a long history as a leader in promulgating ethical safeguards in the conduct of this research; in fact, 40 years ago with the opening of the Clinical Center, the NIH created one of the earliest policies for research involving human subjects.

Investigators must balance their interest in gathering data and answering research questions with society's mandate to protect the rights and safeguard the welfare of research subjects. To help investigators maintain this balance, the NIH has organized a human research protection program (HRPP) which includes policies and procedures related to the protection of human research subjects. This booklet discusses some aspects of NIH's HRPP.

Society has granted a conditional privilege to perform research on human beings. As described in the following pages, the condition is that it must be conducted in a way that puts the rights and welfare of human subjects first.

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1. Introduction

The NIH is the Federal Government's primary agency for advancing knowledge in the biomedical and behavioral sciences in order to understand and treat human diseases. Indeed, it has a long and distinguished history of rapidly applying basic scientific discoveries in the laboratory to the design and conduct of clinical research at the bedside. The NIH has an important obligation to provide leadership, not only in scientific discovery, but also in maintaining high ethical standards in its research activities, particularly those involving human subjects.

Sound ethical practices go hand in hand with scientifically valid research involving human subjects. The NIH assumes that researchers in the Intramural Research Program (IRP) share its commitment to high quality research that promotes the rights and welfare of research subjects. Therefore, the NIH has established a human research protection program (HRPP) to help IRP investigators and research staff understand and fulfill their responsibilities when they conduct or collaborate in research involving human subjects at the NIH or elsewhere.

This brochure provides information about the NIH's HRPP and its policies and procedures for the conduct of research involving people.

2. The Historical, Ethical and Legal Foundations for the NIH's Policies and Procedures Regarding Research With Human Subjects

A brief discussion of the historical origins of the NIH's commitment to protect the rights and welfare of human research subjects is provided in Appendix 1. An appreciation of this historical context is helpful to understanding the reasoning behind the NIH's policies and procedures.

The Belmont Report--Ethical Principles and Guidelines for the Protection of Human Subjects provides the philosophical underpinnings for current Federal laws governing research involving human subjects. The NIH embraces *The Belmont Report* and holds IRP investigators responsible for conducting their research activities in keeping with its principles and guidelines. *The Belmont Report* establishes three fundamental ethical principles that are relevant to all research involving human subjects: Respect for Persons, Beneficence, and Justice. Appendix 2 provides a more comprehensive discussion of these principles and how they are applied to the conduct of research involving human subjects.

Title 45 Code of Federal Regulations, Part 46, Protection of Human Subjects (45 CFR Part 46), embodies the ethical principles of *The Belmont Report*. These regulations apply to all research involving human subjects conducted or supported by the Intramural Research Program (IRP) of the NIH, including involvement by intramural investigators in collaborative activities off the NIH campus. Such activities include "hands-on" involvement with patients or subjects and also indirect involvement, such as analyses of data or human samples (e.g., blood or tissue).

45 CFR Part 46 is not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, these regulations provide a framework in which investigators and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects.

DHHS's Office for Human Research Protections (OHRP) oversees implementation of 45 CFR Part 46 in all domestic and foreign institutions or sites receiving DHHS funds. OHRP requires each institution that conducts or supports research involving human subjects to set forth the procedures it will use to protect human subjects in a policy statement called an "assurance of compliance," commonly referred to as an "assurance." The NIH IRP operates under an OHRP-approved Federal Wide Assurance (FWA). The FWA obligates the NIH to conduct all its research activities involving human subjects consistent with the ethical principles of *The Belmont Report*, the requirements of 45 CFR 46 and other relevant regulations (such as the Food and Drug Administration), and NIH policies and procedures. The FWA covers all research involving human subjects conducted or supported by NIH IRP investigators or in which IRP personnel collaborate, regardless of the site. Failure to comply with the FWA and NIH policies and procedures can lead to loss of research privileges for an individual, a laboratory, an entire research program or the NIH IRP as a whole.

The NIH IRP has organized a human research protection program (HRPP) that establishes roles and responsibilities of NIH institutional officials, the IRP's 14 Institutional Review Boards (IRBs), and researchers and research staff in the conduct of clinical research. The NIH Director assigns overall responsibility for the HRPP to the Deputy Director for Intramural Research (DDIR). Among other responsibilities, the DDIR: (1) establishes and implements IRP policies and procedures in accord with 45 CFR Part 46 and other relevant regulations, requirements and guidelines, and (2) assures that changes in NIH's HRPP are made in response to specific NIH programmatic needs as well as relevant national activities such as recommendations and guidance by national commissions, working groups and regulatory bodies. However, protecting the rights and welfare of human research subjects is a responsibility that is shared by other NIH Institute, Center and Division (ICD) officials: NIH's Institutional Review Boards (IRBs); Laboratory, Branch and Section Chiefs; research investigators, and research personnel.

The NIH IRP's HRPP has policies and procedures regarding: (1) the responsibilities of intramural investigators who conduct, support or collaborate in basic or clinical research activities involving human subjects; (2) the responsibilities of the NIH's IRBs for the review and approval of research activities involving human subjects, and (3) the responsibilities of the NIH's Office of Human Subjects Research (OHSR) in protecting human subjects. These responsibilities are discussed in the next few pages. For more information on the HRPP you may call OHSR (301-402-3444), or go to its website at <http://ohsr.od.nih.gov>.

A. *DEFINITIONS OF "RESEARCH" AND "HUMAN SUBJECTS" :*
Investigators at the NIH are responsible for protecting the rights and welfare of the human subjects who participate in their research. They must also understand the ethical standards and regulatory requirements governing their research activities. "Research" is defined as any systematic investigation designed to develop or contribute to generalizable knowledge. **All intramural investigators who conduct or collaborate in a research activity are responsible for knowing whether or not their research** *involves human subjects.* A "human subject" is a living individual about whom an investigator obtains either (1) data through interaction or intervention with the individual, or (2) identifiable private information. In many cases, the determination of whether a particular research activity involves human subjects is not difficult, but in some cases, the line is blurred. When it is not clear to an investigator whether research activities involve human subjects, he or she is encouraged to seek the advice of others, including Section, Laboratory and Branch Chiefs, IRB Chairpersons, or the OHSR. In questionable cases, final responsibility for determining whether human subjects are involved rests with the OHSR.

B. *SPECIFIC RESEARCH ACTIVITIES THAT ARE NOT SUBJECT TO THE NIH's FWA :*
At the NIH, the following research activities are not considered research involving human subjects: the collection and study of (1) samples from deceased individuals; (2) samples collected for diagnostic purposes only; (3) samples or data that are available from commercial or public repositories or registries; (4) established cell lines that are publicly available to qualified scientific investigators, and (5) self-sustaining, cell-free derivative preparations including viral isolates, cloned DNA, or RNA. However, investigators should be aware that even though research with these types of materials are not covered by the requirements of the IRP's HRPP, it may be subject to other requirements such as rules governing technology transfer.

C. *EXEMPT ACTIVITIES*:

There are six categories of research that, although they involve human subjects, are exempt from the requirements of IRB review and approval. One example is the study or collection of existing records (e.g., pathological specimens), if these sources are publicly available or if the information is recorded by the investigator so that subjects cannot be identified directly or through identifiers linked to the subjects. Other exemptions include some types of research involving taste testing of food, surveys, interviews, use of educational tests and observation of public behavior. The general rationale behind the six categories of exemption is that although the research involves human subjects, it does not expose them to physical, social or psychological risks.

The NIH's Office of Human Subjects Research is authorized to determine whether a research activity is exempt. If an intramural investigator thinks his or her research activity fits into one of the exempt categories, he or she should fill out the form provided by OHSR,* and OHSR will respond in writing. **Investigators should not make determinations about exemptions without consulting OHSR.** Appendix 3 provides a flow chart on how to proceed with the review of a proposed research activity.

D. *ELEMENTS OF A RESEARCH PROTOCOL*:

Investigators conducting or collaborating in research involving human subjects at the NIH or other domestic or foreign sites must receive approval by an Institutional Review Board (IRB) before they begin their study (see Chapter 5). Generally, an investigator provides the IRB with a research protocol, which is a written description of, and scientific rationale for, the proposed research activity. It includes a discussion of the human subject protection issues that are relevant to the study and addresses, at a minimum: the risks to subjects; all procedures which are experimental; the anticipated benefits to subjects, if any; the anticipated number of subjects; the proposed consent document and consent process to be used, and appropriate additional safeguards if potentially vulnerable subjects are to be enrolled. Potentially vulnerable subjects may include the elderly, prisoners, children, cognitively impaired individuals, or people who are economically or educationally disadvantaged. More information on how to prepare a research protocol may be obtained from Laboratory, Branch, and Section Chiefs, the OHSR, or the Clinical Center's publication *Protomechanics*, which is available on request from the Clinical Center's Office of Communications (301-496-2563) or go to <http://www.cc.nih.gov/ccc/protomechanics/index.html>.

*Call OHSR for form "Request For Review Of Research Activity Involving Human Subjects" (301-402-3444) or go to <http://206.102.88.10/nihtraining/ohsrsite/info/Exemption_Form_1.doc>

5. Responsibilities of the NIH's Institutional Review Boards (IRBs)

Research investigators have a fundamental responsibility to safeguard the rights and welfare of the people participating in their research activities. In addition, our society has decided by law that an objective review of research activities involving human subjects by a group of diverse individuals is most likely to protect human subjects and promote ethically sound research. IRBs are generally composed of members with expertise in science, ethics and other non-scientific areas. This diversity fosters a comprehensive approach to safeguarding the rights and welfare of subjects. In their deliberations about proposed research activities, IRB members should take into account the ethical principles of *The Belmont Report*, the requirements of 45 CFR 46, and NIH policies and procedures, as well as the nature and content of the proposed research.

The NIH has IRBs in the following Institutes: NCI (2 IRBs), NIAID, NINDS/NIDCD, NIDDK/NIAMS, NIMH, NEI, NHLBI, NIEHS, NIDCR, NIAAA, NICHD, NIDA, and NHGRI. The Center for Biologics Evaluation and Research (CBER), located on the NIH campus, falls within the purview of an IRB of the Food and Drug Administration.

NIH IRBs evaluate proposed research protocols using the following criteria: (1) the design of the study is consistent with sound scientific principles, ethical norms and regulatory requirements, (2) the protocol satisfies the NIH protocol review standards (see Appendix 4), and (3) the protocol meets NIH policy requirements. In exercising their authority, IRBs may approve, disapprove or table research protocols. Most often, the IRB approves a research study with required changes, referred to as stipulations. However, IRBs are obliged to disapprove any protocol that does not meet the above criteria.

In addition, IRBs conduct continuing review of each approved research protocol or activity at least yearly, although an IRB may request earlier evaluations or updates if it determines that the research presents significant physical, social, or psychological risks to subjects. 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 the IRB's decisions/stipulations/requirements or the NIH's policies and procedures.

Collaboration between intramural investigators and others in the United States and abroad is an important and valuable activity which the NIH supports and promotes. The following guidelines apply in determining whether collaborative research is covered by the requirements of NIH's HRPP.

(1) Collaboration exists if the NIH intramural participant 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.

(2) 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.

Not all collaborations are defined in advance, and there may be subsequent differences of opinion about whether collaboration existed or perhaps developed during the course of research activities. In unclear cases, investigators should contact their IRB Chair or the OHSR. In some cases, further objective third-party review may be necessary.

The requirements of NIH's HRPP apply when an intramural investigator is collaborating in research activities in which subjects are enrolled at non-NIH sites. Such collaborative research activities may require that the non-NIH site negotiate an OHRP-approved assurance and that the research protocol receive review and approval by an NIH IRB *and* an on-site IRB. The latter may be required because institutions often draw from culturally dissimilar subject populations, or are located in different states or other geographical areas with varying ethical, legal, or regulatory requirements for the protection of human subjects.

Guidance on IRB review requirements may be obtained from NIH IRB Chairpersons or the OHSR.

7. The Office of Human Subjects Research (OHSR)

The OHSR reports to the Deputy Director for Intramural Research (DDIR) and was established in 1991 to support the NIH's commitment to conduct innovative human subjects research consistent with sound ethical standards and regulatory requirements. It is a resource in the intramural research community for information and education concerning the regulations and guidelines covering research involving human subjects, and also serves as the NIH IRP liaison with the OHRP.

OHSR staff members are available to answer questions, provide consultation on the design and conduct of research protocols, and participate in educational activities (see back cover).

8. Appendix 1
Historical, Ethical and Legal Foundations For the NIH's Policies and Procedures

Concerns about the ethics of the practice of medicine have a long history but, until the middle of this century, they were mostly centered around the practice of therapeutic medicine, not research medicine. In 1946, 23 Nazi physicians went on trial at Nuremberg for crimes committed against prisoners of war. These crimes included exposure of humans to extremes of temperature, performance of mutilating surgery, and deliberate infection with a variety of lethal pathogens. During the trial, fundamental ethical standards for the conduct of research involving humans were codified into the Nuremberg Code*, which set forth ten conditions that must be met to justify research involving human subjects. The two most important conditions were the need for voluntary informed consent of subjects and a scientifically-valid research design that could produce fruitful results for the good of society.

The Nuremberg Code was reflected in the Declaration of Human Rights and accepted in principle by each of the 51 original signatory nations of the Charter of the United Nations. At that time, most countries, including the United States, had no mechanism for implementing the provisions of the Code. The Clinical Center of the NIH produced the first U.S. Federal policy for the protection of human subjects in 1953. This policy was consistent with the Nuremberg Code in that it gave special emphasis to the protection of healthy, adult research volunteers who had little to gain directly from participation in research. The Clinical Center's policy was innovative in providing a mechanism for prospective review of research by individuals who had no direct involvement or intellectual investment in the research. This was the beginning of the research review mechanism -- the Institutional Review Board -- that is now fundamental to the current system of human subject protections throughout the United States.

In the 1960s Federal funding of clinical research expanded, with a concomitant increase in the number of individuals participating as subjects. Interest in the rights of research

*Available upon request from the Office of Human Subjects Research (OHSR) or on the OHSR website at <http://ohsr.od.nih.gov> (see Ethical Guidelines).

subjects grew not only because of a general increase in America's attention to human rights, but also because of a number of highly publicized clinical research abuses. For example, there were newspaper reports of investigators in New York injecting elderly, indigent people with live cancer cells, without their consent, in order to learn more about the human immune system. Although no apparent harm to subjects occurred, the investigators were cited for fraud, deceit, and unprofessional conduct. In 1966, Henry Beecher, a highly respected physician-investigator from Harvard University, shocked the medical community when he reported that unethical or questionably ethical practices were common in the conduct of human subjects research in many of America's premier research institutions.

The World Health Organization recognized a need for guidelines that were broader in scope than the Nuremberg Code, and *The Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects** was adopted by the World Medical Society in 1964. These guidelines have been revised a number of times, most recently in 1989, and currently are in use throughout the world.

The NIH, under the Directorship of Dr. James Shannon, promoted the development of the first Public Health Service Policy on the Protection of Human Subjects, issued in 1966. At first, the policy applied to extramural activities only, but it was later expanded to cover all human subjects research conducted or supported by the Department of Health, Education and Welfare (HEW). It required prospective review of human subjects research, taking into account the rights and welfare of the subjects involved, the appropriateness of the methods used to secure informed consent, and the risks and potential benefits of the research. The elements of informed consent included the requirement that consent be documented and signed by subjects or their representatives.

*Available upon request from the OHSR or on the OHSR website at <http://ohsr.od.nih.gov>.

Several events in the early 1970s led to renewed and intense efforts in the United States to protect human subjects. Most notable was the revelation that, since the 1930s, approximately four hundred black men in Tuskegee, Alabama, had been involved, without their knowledge, in a lengthy study (the Tuskegee Syphilis Study) on the natural history of syphilis. These men were systematically denied penicillin even after its introduction as the standard treatment for the disease. The Senate Committee on Labor and Human Resources held hearings on this study and on other alleged health care abuses of prisoners and children. The outcomes of these hearings were: (1) enactment of the National Research Act of 1974 requiring HEW to codify its policy for the protection of human subjects into Federal regulations, which it did in 1974; (2) formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and (3) imposition of a moratorium on research conducted or supported by HEW involving live human fetuses until the National Commission could study and make recommendations on it.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which functioned from 1974-1978, evaluated the existing HEW system, recommended improvements to the Secretary, HEW, and issued reports on research involving pregnant women, live human fetuses, prisoners, children, the mentally disabled and the use of psychosurgery. It also issued *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. A major advancement in the development of public policy, *The Belmont Report* provided guidance for distinguishing therapeutic medicine from research, identified three fundamental ethical principles for the protection of human subjects, and illustrated how the ethical principles should be applied to the conduct of human subjects research (see Appendix 2).

In 1979, HEW began the process of revising the 1974 regulations but it was not until 1981 that final Department

(renamed the Department of Health and Human Services -- DHHS) approval was given to Title 45, Code of Federal Regulations, Part 46, Protection of Human Subjects (45 CFR 46). Initially these regulations were applicable only when research was conducted or supported by DHHS, but in June 1991, 45 CFR Part 46 was revised and became the basic policy that now governs all federally supported research.

The Belmont Report--Ethical Principles and Guidelines for the Protection of Human Subjects, which was published in 1979, provides the philosophical underpinnings for the current laws governing human subjects research. Unlike the Nuremberg Code and the Helsinki Declaration, which consist of "guidances" or "rules", *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.

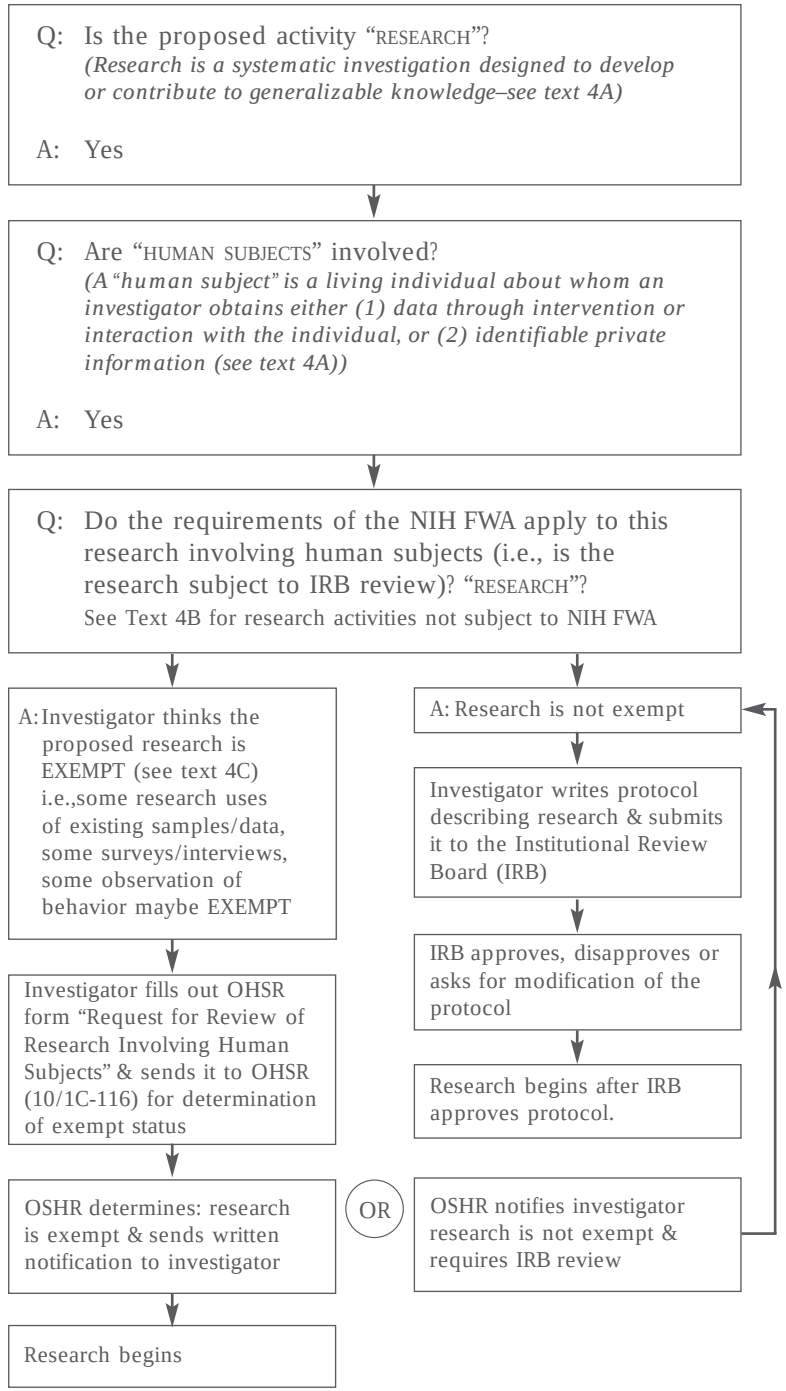
1. The principle of Respect for Persons acknowledges the dignity and autonomy of individuals, and requires that people with diminished autonomy be provided special protection. This principle requires that subjects give informed consent to participation in research. Because of their potential vulnerability, certain subject populations are provided with additional protections. These include live human fetuses, 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, it is necessary to 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 always be justified by the expected benefits of research.

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* 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 3
FLOW CHART FOR DECIDING HOW TO PROCEED WITH THE REVIEW AND APPROVAL OF RESEARCH INVOLVING HUMAN SUBJECTS



APPENDIX 4
IRB PROTOCOL REVIEW STANDARDS
MINIMAL REGULATORY REQUIREMENTS FOR IRB REVIEW, DISCUSSION AND DOCUMENTATION IN THE MEETING MINUTES

REGULATORY REVIEW REQUIREMENT	SUGGESTED QUESTIONS FOR IRB DISCUSSION
1. The proposed research design is scientifically sound & will not unnecessarily expose subjects to risk.	(a) Is the hypothesis clear? Is it clearly stated? (b) Is the study design appropriate? (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.	(a) What does the IRB consider the level of risk to be? (See risk assessment guide p.24.) (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 p.24.)
3. Subject selection is equitable.	(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.	(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).	(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. Risks to subjects are minimized.	(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.	(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?

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)**).

Select risk category for protocol under review by the IRB:

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

2. _____The research involves more than minimal risk to subjects.

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.

Select appropriate benefit category for protocol under review by the IRB:

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.

1. For help to decide if your research involves human subjects, discuss it with:
   - your Section, Branch, or Laboratory Chief,
   - your IRB Chair,
   - your Clinical or Scientific Director, or
   - OHSR (301-402-3444)

2. To determine whether your proposed research activity is exempt from the requirement of NIH IRB review and approval:
   - discuss it with your Section, Branch, or Laboratory Chief, AND
   - Complete the form entitled "Request for Review of Research Involving Human Subjects" at (http://ohsr.od.nih.gov) and send it to OHSR (Building 10, Room 1C116) for determination of exempt status.

3. For assistance in writing a research protocol:
   - Ask your Section, Branch, or Laboratory Chief, and
   - See "Protomechanics – A Guide to Preparing and Conducting a Clinical Research Study" at (http://www.cc.nih.gov/cc/protomechanics/index.html)

4. For help in planning a research study with challenging or complex ethical or regulatory considerations consult:
   - your Section, Branch, or Laboratory Chief,
   - your IRB Chair,
   - OHSR (301-402-3444), or
   - The Clinical Center's Department of Bioethics (301-496-2429)

5. For educational materials or to arrange an educational program about human subject protections:
   - Call OHSR (301-402-3444)