The Human Research Protection Program at the NIEHS:

A Guide for Investigators

NIEHS IRB Reference Guide

Version 1.0

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Other Guides:

NIEHS Epidemiology Branch Reference Guide

NIEHS Non-Epidemiology Branch Reference Guide

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Table of Acronyms

Acronym	Meaning
AP	Administrative procedure
BC	Branch Chief
CAC	NIEHS Clinical Advisory Committee
CC	NIH Clinical Center (NIH Campus in Bethesda)
CD	NIEHS Clinical Director
COI	Conflict of interest
DSMB	Data and safety monitoring board
EB	Epidemiology Branch
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HSR	Human Subjects Research
IRB	Institutional Review Board
LAR	Legally Authorized Representative
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
OHRC	Office of Human Research Compliance (NIEHS)
OHSR	Office of Human Subjects Research (NIH)
OMB	Office of Management and Budget
OPS	Office of Protocol Services
OSD	Office of the Scientific Director
SD	Scientific Director, NIEHS Division of Intramural Research
SOP	Standard Operating Procedure

Introduction

The purpose of this document is to provide practical and policy guidance for National Institute of Environmental Health Science (NIEHS) investigators concerning the protection of the rights and welfare of human subjects in research. This document does not cover every aspect of human subjects research (HSR). For example, it does not address scientific review, resource review, or conflict of interest (COI) review in significant detail. Other documents deal with these issues. This document includes or encompasses some policies and procedures developed specifically for the NIEHS Human Research Protection Program (HRPP) [such as the Office of Human Research Compliance's (OHRC) Administrative Procedures (APs)], some that apply to all National Institutes of Health (NIH) Human Research Protection Programs (HRPPs) [such as the Office of Human Subjects Research's (OHSR) Standard Operating Procedures (SOPs)] and some that apply to all institutions that receive federal funding [such as The Common Rule, 45 CFR 46]. This document compliments but does not replace other documents that it is based on. This document draws from or references the following documents:

1. OHSR, SOPs for all IRBs. http://www.nihtraining.com/ohsrsite/irb/procedures.html
2. OHSR, Information Sheets. http://www.nihtraining.com/ohsrsite/info/info.html
3. NIH's HRPP, NIH Policy Manual 3014. http://www1.od.nih.gov/oma/manualchapters/intramural/3014/
4. 45 CFR 46 (The Common Rule). http://www.nihtraining.com/ohsrsite/guidelines/45cfr46.html
5. The Belmont Report. http://www.nihtraining.com/ohsrsite/guidelines/belmont.html
6. OHRC APs. .....[website is under development]

Nothing in this document should be interpreted as conflicting with the above documents or applicable federal or state laws. Sources for guidance will be referenced, where appropriate.

***Note to the reader**: The word "protocol" has two meanings in this document: 1) a research project involving human subjects, 2) a plan for conducting research with human subjects including objectives, methods, data analysis, inclusion criteria, etc. It should be apparent from the context which meaning is being used.*

Human Research Protection Programs at NIH and NIEHS

The Office for Human Research Protections (OHRP)

OHRP protects the rights, welfare, and well-being of subjects involved in research conducted or supported by the Department of Health and Human Services (DHHS), including the NIH, and helps ensure that such research is carried out in accordance with the regulations described at 45 CFR part 46. OHRP provides leadership in the protection of human subjects participating in such research by providing clarification and guidance, developing educational programs and materials, and maintaining regulatory oversight. The NIH has entered an agreement with OHRP known as a Federal Wide Assurance (FWA) in which it promises that all human subjects research conducted by its investigators will comply with the 45 CFR 46 (also known as The Common Rule) and the Belmont Report. The Deputy Director of Intramural Research (DDIR) is the signatory on the FWA. OHRP link: http://www.hhs.gov/ohrp/

The Office of Human Subjects Research (OHSR)

OHSR oversees the HRPP in the NIH's intramural research program. OHSR reports directly to the Deputy Director of Intramural Research (DDIR). OHSR helps researchers, research staff, Institutional Review Boards (IRBs) and others understand and comply with the ethical guidelines, regulatory requirements and NIH policy and procedures for research involving human subjects. OHSR assists with 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. It 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. It 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. OHSR also works closely with the NIH's 18 IRBs to assist them to fulfill their mandate to protect the rights and welfare of human subjects. OHSR link: http://ohsr.od.nih.gov/

The Office of Protocol Services (OPS)

OPS provides centralized support services for clinical researchers at NIH. The service efficiently moves protocols through an approval pathway process. OPS staff members assist with individual protocols and consults on issues related to the regulatory requirements for the protection of human subjects in research and the IRB protocol submission requirements. OPS maintains a data repository for the NIH intramural research program containing more than 1,600 active protocols and nearly 2,100 protocol consent/assent documents. 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, submitting, and monitoring protocols. ProtoType includes electronic links to IRB forms, policies and procedures. Starting in 2009, NIEHS investigators will be able to use ProtoType.

Link to ProtoType: https://prototype.cc.nih.gov/prototype10/contents/login/pw_login_screen.aspx

OPS reports to the Director of the NIH Clinical Center. OPS link:
http://intranet.cc.nih.gov/ops/index.html

NIEHS Office of Human Research Protection Program

The NIEHS HRPP consists of two components: the IRB and OHRC. Briefly, the IRB is responsible for reviewing and approving HSR conducted by NIEHS investigators and OHRC provides administrative support for the IRB and ensures that NIEHS HSR complies with applicable laws, regulations, policies, and guidance. The Chair of the NIEHS IRB reports to the DDIR and the Director of OHRC reports to the NIEHS Clinical Director (CD). The NIEHS IRB and OHRC have established some of their own policies and procedures. The IRB and OHRC are both responsible for protecting the rights and welfare of human subjects involved in research at the NIEHS. The IRB Chair and OHRC Director work together to develop and maintain a quality program that protects human subjects and is fully compliant with federal regulations and NIEHS/NIH/DHHS guidelines. The NIEHS IRB usually meets on the second Thursday of each month. NIEHS IRB link (includes current meeting schedule):
http://www.niehs.nih.gov/about/orgstructure/boards/irb/index.cfm

1. OHRC link: .....[website is under development]
2. IRB Chair: Dr. David Resnik (resnikd@niehs.nih.gov)
3. OHRC Director: Dr. Joan Packenham (packenhm@niehs.nih.gov).

Table 1: Human research protection programs at the DHHS, NIH, and NIEHS

Organization	HRPP Component
DHHS	Office of Human Research Protections
NIH	Office of Human Subjects Research
	Office of Protocol Services
NIEHS	Institutional Review Board
	Office of Human Research Compliance

Guidance for Investigators

Investigator responsibilities

From the NIH Policy Manual 3014:

1. 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 PI for each protocol. PIs must be qualified members of the credentialed senior, junior, research or adjunct staff, registered nurses, pharmacologists, psychologists, or other health professionals. Consultants and students may not act as PIs.
2. 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 PI. 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.
3. Associate Investigators (AIs). AIs who are staff in the NIEHS 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.
4. Medical Advisor (MAs). When the PI is not a member of the NIEHS junior or senior staff, or when the Clinical Director, IRB or Director NIEHS, consider it warranted, a Medical Advisor must be identified in the protocol. The Medical Advisor must be a member of the NIEHS junior or senior medical staff.
5. 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.

Educational Requirements

From NIH Policy Manual 3014:

1. 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. Link to course: http://ohsr.od.nih.gov/researcher/intro.php
2. PIs on all NIEHS protocols must complete the NIH 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. Link to course: http://www.cc.nih.gov/training/training/crt.html

Additional policies developed for NIEHS' HRPP:
All researchers and staff are strongly encouraged to take part in continuing education and training activities each year, such as bioethics seminars at the NIEHS or local institutes, and national conferences or workshops. The Human Subjects Research Bulletin (a newsletter, published twice each year) may also contain educational items for investigators. From time to time, the IRB may require special education/training on specific items of urgent importance in HSR. Researchers may have to complete other NIH-mandated education/training requirements, such as ethics training, responsible conduct of research training, and so on.

Submitting a new human research protocol

Is the activity human subjects research?

For the human subjects research regulations to apply to an activity at the NIEHS, it must be the case that the activity is considered to be 1) research that 2) involves human subjects. Research is defined as: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102d)." Some types of data collection that involve human beings, such as quality improvement projects, are not considered to be research because they are not designed to develop or contribute to generalizable knowledge. A human subject is defined as: "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (45 CFR 46.102f)." Some types of research activities that involve people may not actually involve human subjects. For example, research on public documents, such as court cases and birth and death records, involves information about people, but not human subjects. Research on data or biological samples in which the human subject is not identifiable may also not be considered HSR, and research on data or biological samples in which the individual is no longer living is not HSR. Talk to the IRB Chair or the OHRC Director if you have any questions about whether your proposed research activity is classified as HSR.

Exempt research

If the activity is HSR, then the activity may need to be reviewed by the NIEHS IRB. Most, but not all, HSR at the NIEHS must be reviewed by the IRB. HSR that does not require IRB approval is known as exempt research, because it is exempted from 45 CFR 46. Neither the investigator nor the NIEHS IRB can determine whether research qualifies as exempt. OHSR makes that determination. Link to form to submit to OHSR: http://ohsr.od.nih.gov/info/pdf/requestforReview.doc

The following are some types of research that would qualify as exempt (from 45 CFR 46.101b):

1. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research

could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

2. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
3. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exempt research often involves collaborations between NIEHS investigators and investigators at other institutions. For example, an NIEHS investigator may analyze human biological samples or data provided by an investigator at a university. Investigators should contact the IRB Chair or OHRC Director if they think their proposed research may qualify as exempt. OHRC will provide investigators with a form to request an exemption or the form can be downloaded at the following website: http://ohsr.od.nih.gov/info/pdf/requestforReview.doc. The form should be filled out and sent electronically to OHRC at NIEHS-OfficeofHRC@niehs.nih.gov. OHRC will log receipt of the submission, review the form, resolve any issues with the PI, and submit the form with supporting materials to OHSR. OHSR usually acts quickly on exemption requests (two weeks or less). OHSR may request additional information from the investigator. If OHSR grants an exemption, they will send a memo to the investigator, and the investigator can begin the research. The investigator should send a copy of the approval memo to OHRC. The investigator does not need to interact with OHSR or the NIEHS IRB or OHRC any longer, unless he/she decides to make changes in the research that would make it no longer qualify as exempt. If this occurs, he/she must submit the protocol to the IRB for review. See Figure 1 on page 17.

Non-exempt research

If the research is not exempt, it must be submitted to the IRB for review. Before a protocol can be reviewed by the IRB, it must undergo several other types of review, including preliminary proposal review, scientific review, resource reviews (if appropriate), and COI review (see below). NIEHS policies and procedures for these pre-IRB reviews are contained in the following two documents: 1) The Review and Approval Process for NIEHS Clinical Studies - NIEHS Non-Epidemiology Branch Reference Guide; and 2) The Review and Approval Process for NIEHS Clinical Studies - NIEHS Epidemiology Branch Reference Guide. Investigators should contact the NIEHS Clinical Director or the OHRC staff to obtain more information about COI review, scientific review, and other pre-IRB reviews.

Once a protocol has undergone the appropriate pre-IRB reviews, it can be submitted to the IRB. The protocol must be submitted at least 3 weeks prior to the IRB meeting at which it will be reviewed. (In the future, this deadline may become less than 3 weeks when the IRB submission system becomes paperless.) Materials required for submission include:

- The completed NIH-1195 form. PDF version: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/1195.pdf WORD version: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/niehs_irb_standard_format_04.doc
- The protocol in standard format Link: [Under development]
- Informed consent documents
- Advertisements
- Scientific reviews
- The completed NIH-2686 form: Designation of reimbursement for travel and subsistence for NIH clinical intramural research protocol: [Under development]. See Payments to Research Subjects in Informed Consent Guidance for further discussion of reimbursement issues.
- Conflicts of interest reviews. Investigator financial holding form: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/pfc-form.pdf
- Other supporting documents.

Investigators should work with OHRC staff to prepare a complete submission. Investigators are encouraged to consult with the IRB Chair or OHRC Director concerning human subjects protection issues with their protocol, 1-2 weeks prior to submission.

PIs are required to identify in their protocols any Principal or Associate Investigator or Medical Advisor involved in the protocol who has an equity or consultative relationship with a non-NIH entity related to the protocol which might be considered a real or an apparent conflict of interest. The financial interests of the NIH employees named on a protocol must be reviewed to confirm that no conflict of interest exists between investigators' official duties on the protocol and their personal or imputed financial interests. The NIEHS Deputy Ethics Counselor in the NIEHS Ethics Office conducts COI review. COI review usually takes six weeks, and must be completed before the investigator can begin research. To provide enough time for COI review to take place, investigators should submit their forms for COI review two weeks prior to IRB review. Information concerning COI review: http://inside-www.niehs.nih.gov/omhrmb/protocols.htm.

Some PIs at the institute are not permitted to submit their protocols to the NIEHS IRB due to a potential conflict of interest. These include the NIEHS Director, the NIEHS Scientific Director and the NIEHS Clinical Director. These protocols may be submitted to another NIH IRB for review and approval.

The protocol must be in the following standard format. Link to PDF fill-able form: [Under development]

From OHRP Information Sheet 5:

1. Précis. In 400 words or fewer, provide a description of the objectives, study population, design, and outcome parameters.
2. Introduction. Describe the background, including human subject or animal research and references that are relevant to the design and conduct of the study. Where new techniques or procedures are to be used, a description of preliminary or early work should be provided. If an FDA Investigational New Drug (IND) is to be used, animal data on the drug should be included. If the study is one for which a Clinical Investigator's Brochure (CIB) is provided, one copy of the CIB must be available to the IRB

when the protocol is reviewed. A summary of the relevant features of the CIB should be included in the protocol.

3. Objectives. State the objectives of the study, whenever possible, as hypotheses.
4. Study Design and Methods. Describe the involvement of human subjects including initial evaluation procedures and screening tests, phases, procedures and sequence of the study. Separate standard and experimental aspects of the study as much as possible. Describe alternatives to experimental therapy if they exist. Give detailed procedures for treatment, dose adjustments, etc. Describe the randomization procedure, if applicable. Address the experience of investigators if procedures are to be performed for which the investigators have not been specifically credentialed.
5. Inclusion and Exclusion Criteria. These must be included in the protocol.
6. Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study. Describe the types, frequency and duration of tests, admissions, outpatient visits. Consider specifying a monitor if the study involves a blinded design. Define stop points and criteria for withdrawing subjects from the study.
7. Analysis of the Study. Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons.
8. Human Subject Protections.
    a. Rationale for Subject Selection. The protocol must include (a) a rationale for research subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied; (b) strategies/procedures for recruitment (including advertising, if applicable); and (c) justification for exclusions, if any. If the protocol involves subject enrollment at multiple sites, describe plans for ensuring appropriate IRB review and approval at each site. Explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, cognitively impaired individuals, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. Discuss what, if any, procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risks (physical, psychological, etc.) as research subjects.
    b. Evaluation of Benefits and Risks/Discomforts. Describe the potential benefits to subjects or to others that may reasonably be expected from the research. If volunteers are involved, specify compensation, if applicable. Describe any potential risks -- physical, psychological, social, legal, or other -- and assess their likelihood and seriousness. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects. Describe the procedures for protecting against or minimizing any potential risks, such as violations of confidentiality, and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects, i.e. data a safety monitoring plans. Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.
    c. Consent and Assent Processes and Documents. Describe the consent procedures to be followed, including the circumstances in which consent will be sought and obtained, who will seek it (e.g., contract staff, Principal Investigator, etc.), the nature of the information to be provided to prospective subjects, and the method of documenting consent. The proposed consent document

must be attached. It should be written in the second person, in language understandable to someone who has not completed high school. Children are generally not legally empowered to give consent, but depending on their age, they may have the ability to give assent ("assent" means a child's affirmative agreement to participate in research). Every protocol involving children (those individuals under age 18) should include a discussion of how assent will be obtained for the particular study. The IRB will determine whether the children are of sufficient age to sign an assent form.

d. Confidentiality protections. Describe the steps that will be taken to protect the confidentiality of the research data and protect the subjects' privacy. Discuss the procedures for handling, storing, transferring, using, sharing, or destroying human biological samples, if applicable.

9. Adverse Event Reporting and Data Monitoring - Provide a plan for reporting adverse events to the IRB. Also, describe the provisions for monitoring the data collected to ensure the safety of subjects.
10. Collection and Storage of Human Specimens or Data - All NIH IRB-approved research protocols in which IRP researchers intend to collect and store human specimens or data must include a written description of the intended use of the samples; how they will be stored; how they will be tracked; what will happen to the samples/specimens/data at the completion of the protocol, and what circumstances would prompt the PI to report to the IRB loss or destruction of samples. Remuneration/Compensation - Describe the rationale for and amount of any proposed compensation.
11. References. Include selected references which highlight methods, controversies, and study outcomes.
12. Additional considerations (e.g., ionizing radiation; collaborative research; IND, other. Discuss contract or study conduct arrangements. State if these considerations do not apply). If a study is being conducted under contract, describe the role of contract staff as well as NIEHS staff. Discuss the role of collaborating institutions.

Table 2: IRB submission timelines

Time	**Deadline/event**
Weeks prior to IRB meeting*	Scientific review and other reviews (refer to relevant pre-IRB review documents)
4-5 weeks prior to IRB meeting	Discuss submission with IRB Chair or OHRC Director
4 weeks prior to IRB meeting	Submit COI review materials to NIEHS ethics office
3 weeks prior to IRB meeting**	Deadline for submitting a new protocol
1 week after IRB meeting***	Investigator receives memo from IRB Chair via OHRC
2 weeks after IRB meeting****	OPS completes documentation review if protocol has been approved by the IRB; research can begin
30 days after IRB meeting	Deadline for submitting responses to stipulations that can be reviewed by expedited review

*Varies, depending on the type of review.

**May become less than 3 weeks when the IRB submission system becomes paperless.

***May be less than 1 week.

****Typical time period; some variation may occur.

Criteria for review of human subjects research

In deciding whether to approve a study, renew a study's approval, or approve an amendment to a study, the IRB (or Chair) will consider the following criteria, which also apply to full board approvals.

From 45 CFR 46.111:

1. Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards should be included in the study to protect the rights and welfare of these subjects.

In addition to these criteria, the IRB/Chair will also consider whether the study is consistent with the three principles from the Belmont Report—respect for persons, beneficence, and justice—and whether the study has scientific validity and merit. Since protocols must undergo scientific review before being submitted to the IRB, scientific issues will normally not be a major concern at IRB review. However, the IRB may consider scientific issues during its review, since the design of a study may have an impact on whether it meets the criteria for IRB review or the Belmont Report's ethical principles. Additionally, the IRB may need to address other regulations/laws that pertain to the research, such as the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) or state statutes.

The IRB Chair has only three decision options for expedited review: 1) approve as is; 2) approve with stipulations that can be reviewed by the Chair; or 3) table. The Chair cannot disapprove a protocol. If the protocol is approved with stipulations, the investigator will need to make the required changes to obtain approval. Once the study is approved, the investigator will receive a memo from the IRB Chair and the study will be forward to OPS for processing. OPS will verify that all the correct documentation is in place. The investigator may begin research once he/she receives a memo from OPS. See Figure 1, page 17, for additional details.

Expedited review

If the research is considered to be minimal risk, then the protocol may not need to be reviewed by the full IRB. It can be reviewed by the IRB Chair or designee. Minimal risk is defined as: "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102i)."

OHSR has determined that the following research activities qualify as minimal risk (From OHSR SOPs):

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.) (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where

medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Some research activities not on this list may qualify for expedited review because they are judged to be minimal risk studies. Also, some research on this list may not be reviewed by expedited review for policy reasons. OHSR has set a policy that requires all studies that involve genetic testing have full board review. Also, the IRB Chair may decide that a minimal risk study should be sent to the full board for review because it raises ethical or human subjects issues that should be considered by the full board.

Full board review

If the study cannot be approved by expedited review, it will be reviewed by the full board. The copies of the protocol and other materials will be distributed to IRB members. One IRB member will be designated as the primary reviewer, and another as the secondary reviewer. Primary and secondary reviewers may ask the investigator questions prior to the meeting, to better understand the nature of the research and/or address any human subjects concerns. Investigators are encouraged but not required to attend the meeting at which their protocol is reviewed. If an investigator attends the meeting, he/she can present his/her protocol to the board and answer questions. He/she must leave the meeting prior to the board's discussion and vote. During its discussion, the IRB will consider whether the study should be approved, the approval period (no more than one year), and whether there are any changes the must be made to the protocol before it can be approved (i.e. stipulations). The IRB may also may some recommendations, which are changes the investigator may consider making, but is not required to make. The outcome of this discussion falls into one of five categories:

1. Approval with no stipulations. This is a rare occurrence for new protocols since even experienced investigators have minor problems with the protocols or consent forms that need to be addressed. If

the protocol is approved with no stipulations, the investigator will receive a memo from the IRB within 5 business days, and paperwork will be sent to OPS for processing. OPS will verify that all the correct documentation is in place. The investigator may begin research once he/she receives a memo from OPS (usually about 10 business days after it receives the paperwork from the IRB). Approval with no stipulations is common for renewals of research (see below).

2. Approval with stipulations that can be reviewed by the IRB Chair or designee. The IRB has decided to approve the protocol once the investigator makes the required changes, and the IRB has determined that the required changes are minor (i.e. they do not require substantive judgment by the reviewer), so that the changes can be reviewed by the IRB Chair or designee. A memo will be sent to the investigator describing the outcome of the meeting and the reasons for the stipulations within five business days. The investigator has 30 days to respond (in writing) to the stipulations. Once the investigator responds and the Chair or designee has determined that the investigator has made the required changes, approval is granted. A memo will be sent to the investigator and the protocol will be sent to OPS for processing. OPS will verify that all the correct documentation is in place. The investigator may begin research once he/she receives a memo from OPS.
3. Approval with stipulations that must be reviewed by the full board (deferred approval). The IRB has decided to approve the protocol once the investigator makes the required changes, but the IRB has also determined that the required changes are more than minor, so that they cannot be reviewed by the IRB Chair or designee. A memo will be sent to the investigator describing the outcome of the meeting and the reasons for the stipulations within five business days. The investigator must make corrections to the protocol package, which will be reviewed at the next IRB meeting if the investigator submits these corrections at least seven business days prior to that meeting. The outcome of the meeting could be approval with no stipulations or approval with stipulations (see above).
4. Tabled. The IRB has determined that there is insufficient information or documentation to make a decision. A memo will be sent to the investigator describing the outcome of the meeting and the reasons for tabling within five business days. Hopefully, this will be a rare occurrence because OHRC will help investigators prepare their protocol packages so as to avoid this outcome. The investigator should work closely with the OHRC to provide the additional information or documentation to prepare to protocol for submission at another IRB meeting.
5. Disapproval. This is a very rare outcome, and indicates that a study is so flawed (in terms of human subject protections) that it cannot be approved as written. A memo will be sent to the investigator describing the outcome of the meeting and the reasons for disapproval within five business days.

Reconsiderations

If the IRB disapproves a research protocol, the investigator may write a letter to the IRB Chair asking the IRB to reconsider its decision. Reconsiderations will be addressed at a full board meeting. The IRB retains the final authority for approval of proposed research with human subjects. Institutional officials cannot override the IRB's decision and approve research that the IRB has not approved. However, institutional officials can decide not to approve or fund research that the IRB has approved.

Continuing review

As mentioned earlier, a protocol will be approved for a specific period of time (usually one year). To continue conducting research, the investigator must submit a continuing review form to the IRB in time

for the review to take place before the continuing review deadline. There is a form for renewing a protocol. Link: http://www.nihtraining.com/ohsrsite/irb/Attachments/6-5_1195-1_0906_Fillable.pdf

The continuing review date is set by the IRB. If the protocol is approved or approved with stipulations that can be reviewed by the Chair, the continuing review date is generally one year from when those approvals occur. If the approval occurs with stipulations that cannot be reviewed by the Chair (i.e. approval is deferred to the full board), the continuing review date is generally one year from when the protocol is approved at a subsequent IRB meeting. If the continuing review can be reviewed on an expedited basis (see below), the IRB must receive the submission at least 30 days prior to the continuing review date. If the continuing review requires full board review, the IRB must receive the submission at least 50 days prior to the IRB meeting that immediately precedes the continuing review date. OPS will send two reminders to the investigator, at 120 days before the continuing review date and at 60 days before the continuing review date. OHRC will also send reminder memos to the investigator at 30, 60, and 90 days before the review needs to be submitted. Depending on the nature or stage of the research, the continuing review may be reviewed by the full board or by the Chair or Designee. Protocols that can be renewed by expedited review include protocols where (from OHSR SOPs):

1. The research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or
2. No subjects have been enrolled and no additional risks have been identified; or
3. The remaining research activities are limited to data analysis; or
4. The research is conducted under an investigational new drug application or investigational device exemption where the other expedited review categories do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The outcome of this review may be similar to the outcome of the review of a new protocol, i.e. approved as is, approved with stipulations, etc. The reviewer will apply the same criteria for approval that are used for approving a new protocol (see above). The continuing review date may vary from year to year, depending on actions taken by the IRB and investigator.

Some of the required materials to be submitted with the form include:

1. Continuing Review Checklist. http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/cr-checklist042808.pdf
2. Copies of current consent documents
3. Subject Accrual Tables
4. Cumulative subject enrollment (gender by ethnicity)
5. Subject enrolled since the last review (gender by ethnicity)
6. Link to table form: http://ohsr.od.nih.gov/irb/Attachments/6-6_Summary_Minority_Inclus.doc
7. Short Narrative Statement to the IRB, including:
   a. A concise statement regarding protocol progress to date,
   b. The reason(s) for continuing the study,

c. Any scientific developments that bear on the protocol, especially those that deal with risks, burdens or benefits to individual subjects,
d. Changes in the protocol which are substantive (These must be received and approved before they can be implemented by the IRB.),
e. Summary of all amendments to the protocol approved during the past review period.

8. Provide a copy of the current protocol which includes all amendments.
9. Clearance of NIH Investigator Personal Financial Holdings Form (PFC) for all investigators on the study, including documentation off-site investigators if a multi-site study
10. Documentation of an outside IRB approval if a multi-site study.

Investigators should contact the OHRC staff about the requirements for protocol renewal. As with other IRB actions, once continuing review is granted by the IRB, a memo will be sent to OHSR, and if OHSR approves, the investigator will receive a memo from OHSR through OPS. See Figure 1 on page 17.

Table 3: Continuing review dates/deadlines

Time	Deadline/reminder
Continuing review date	Set when protocol is approved
30 days prior	Deadline for submitting expedited continuing reviews
50 days prior	Deadline for submitting full board continuing reviews
60 days prior	Reminder from OPS
60-80 days prior	Reminder from OHSR
90-110 days prior	Reminder from OHSR
120 days prior	Reminder from OPS
120-140 days prior	Reminder from OHSR

What happens if the protocol expires?

From OHSR Information Sheet 9:

In keeping with federal regulations, the NIH expects all protocols to complete IRB review and approval by their continuing review due date. IRBs and PIs must plan ahead to meet required continuing review dates. If by the specified review date the IRB has not completed its review and approval, the IRB approval for the study expires. Upon expiration, enrollment of new subjects cannot occur and all research activity, including subject follow up, study interventions, and data collection and analysis must stop. In the extremely rare circumstance when the investigator is actively pursuing renewal with the IRB and the IRB believes that an overriding safety concern or ethical issue is involved, the IRB may permit study activities to continue for the brief time required to complete the review process. Within 24 hours of expiration of IRB approval, the OPS will block accrual of new subjects. An e-mail notification of this action will be sent to the PI, IRB Chair, IRB office, OHSR and the IC Clinical Director. This notice and all correspondence about an overdue protocol from the OPS and the IRB will be maintained in the PI's protocol file and in the IRB office. Protocols that have not been submitted for review to the IRB by their expiration date are automatically terminated. Protocols which have been reviewed by the IRB by their expiration date but which have not completed their approval within 30 days of notification of expiration

are terminated by the IRB. The PI, IC Clinical Director, OHSR, OPS, and the Director of the Clinical Center will be notified of such action. Upon notification of termination, the PI must submit to the IRB proposed procedures for withdrawal of currently enrolled subjects that takes into consideration their rights and welfare. Reactivation of a terminated study requires submission of a protocol to the IRB for initial review.

Terminating a protocol

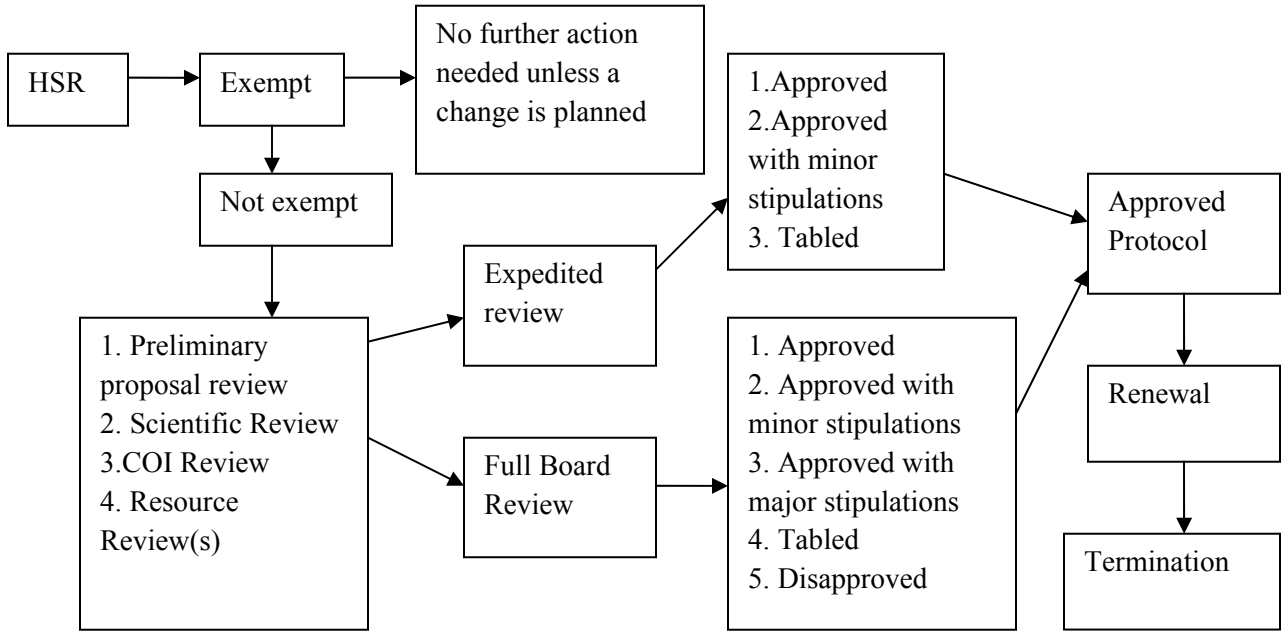
When the investigator completes all research activities, including all data analysis, the investigator may terminate (or close) the protocol by submitting a continuing review form to the IRB and checking the "terminate protocol" box. The form should include a letter and attachments that addresses the following:

1. Brief summary of protocol purpose
2. Reason for termination
3. Summary of accrual/ subject withdrawals for the previous year and for the entire study. Attach Accrual Table.
4. Summary of serious and non-serious adverse events for the life of the protocol (if applicable).
5. Plans for withdrawing subjects and transferring care (if applicable).
6. Results from the study
7. Data and sample disposition and/or storage:
    a. List types of data and samples stored, as well as storage location
    b. List protocol under which data/sample analysis will continue, if applicable
    c. If samples will be destroyed, state which samples and the method of disposal
8. Publications
9. Other Documents or reports

List or briefly summarize other reports, correspondence, or approvals (e.g. DSMB, FDA, outside collaborators, outside IRB documentation, tech transfer agreements).

A protocol can also be terminated by the IRB. The IRB may terminate a protocol for serious or continuing non-compliance with federal regulations or other safety concerns. As noted above, a protocol may be terminated if it is not renewed in time. See Figure 1, below.

Figure 1: The Life of an HSR Protocol



Participation in off-site protocols

From NIH Manual 3014:
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 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.

Amendments

Investigators must obtain IRB approval for any changes they plan to make to an approved protocol and supporting documents, such as changes in study procedures, subject accrual targets, consent forms, co-investigators, advertisements, brochures, etc. Investigators should submit a memo requesting an amendment to the IRB Chair, describing the proposed amendment and the reason(s) for it. The documents to be amended should also be submitted, with proposed changes indicated. If the amendment involves only a minor change, the Chair will review it, and if approval is granted, a memo will be sent to the investigator and paperwork to OPS for processing. If the amendment involves a more than minor change, it must be submitted to the full IRB for review. If the IRB approves the amendment, a memo will be sent to the investigator and paperwork to OPS for processing. A minor change is defined (from the OHSR SOPs) as i) a change that does not adversely alter the risk-benefit profile of the study; ii) a change that does not potentially affect the willingness of current subjects to remain in the study; and/or iii) a change that does not alter the scientific validity of the study design. Examples of minor changes may

include, but are not limited to, change of investigator; addition of minimal risk procedure(s); addition of laboratory tests that increase subject safety. Investigators should consult with the IRB Chair or OHRC staff concerning submissions of amendments. OHRC will periodically monitor research to ensure that all changes that have taken place have been approved by the IRB as amendments.

Unanticipated problems: adverse events, protocol deviations and violations

Research institutions are required to have procedures for reporting to the IRB "unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance…or the requirements or determinations of the IRB (45 CFR 46.103b(5))." 45 CFR 46 does not define "unanticipated problems…"

According to OHRP Guidance (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm), an "unanticipated problem involving risks to subjects or others" includes all of the following characteristics:

1. Event is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Event is related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Event places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHSR's SOPs require investigators to promptly report unanticipated problems involving risks to subjects or others to the IRB. According to the SOPs:

PIs are responsible for reporting promptly to the IRB any unanticipated problems involving risks to subjects or others, or unexpected serious harm to subjects and others. When the event is serious, written reports (using the NIH form and in accord with the NIH reporting timeline) are submitted by the PI for evaluation to:

1. The IRB;
2. The Institute Clinical Director who notifies the Institute leadership and the Director, CC, if the protocol is conducted in the NIH CC;
3. The FDA and/or non-NIH sponsor, Institutional Biosafety Committee, or Office of Biotechnology Activities as necessary, and when NIH policy requires.

The IRB judges whether the event was unexpected, and the severity and relatedness of the adverse event to the study, and records this judgment in the meeting minutes. In the event of unexpected serious harm, the IRB may choose to modify, suspend, or terminate the protocol and/or consent. It communicates this decision in writing to the PI, the Institute Clinical Director, and OHSR, and documents the decision in the minutes. The Director of the CC, through OPS is notified of terminations and suspensions for protocols

that are conducted at the NIH CC. OHSR evaluates the IRB's assessment of the event and forwards the report to the Office for Human Research Protections (OHRP) as necessary.

Link to forms and additional policy guidance and timelines:
http://ohsr.od.nih.gov/adverse/index.html

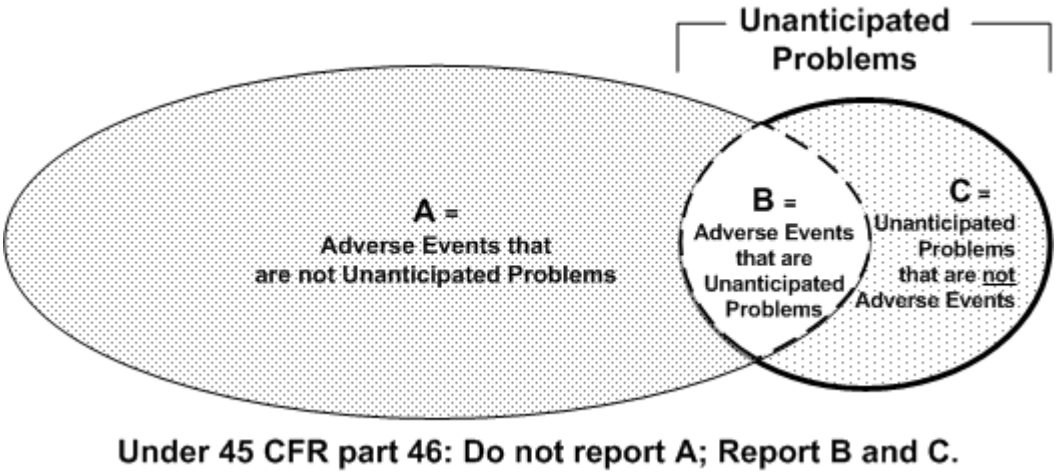
Adverse events

Some types of unanticipated problems are also adverse events. The term "adverse event" does not occur in 45 CFR 46; it comes from the FDA regulations. A common definition of an adverse event is "any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen http://ohsr.od.nih.gov/irb/Attachments/5-10_Serious_Adverse_Event_Rep.htm ."

Not all adverse events need to be reported promptly to the IRB: only adverse events that are serious and unexpected need to be reported. Other adverse events can be reported at the time of continuing review (OHRP SOPs). Link to reporting form:
http://ohsr.od.nih.gov/irb/Attachments/5-10_Serious_Adverse_Event_Rep.htm

It is also important to note that not all unanticipated problems are adverse events: in fact, most are not. See the diagram below for the relationship between adverse events and unanticipated problems (from OHRP Guidance):

Figure 2: Adverse Events vs. Unanticipated Problems (from OHRP guidance)



Principal Investigator (PI) responsibilities for adverse events

From OHSR SOPs:

1. The PI must propose and justify in all clinical research protocol applications a plan for collection, monitoring and analysis of adverse events. The IRB will determine whether the data and safety monitoring plan is appropriate (i.e., commensurate with the level of risk involved in the specific clinical research project).
2. Unless otherwise specified on the protocol and approved by the IRB, all serious adverse events must be reported by the PI verbally and in writing to the Clinical Director using the attached form. Serious adverse events, both related and unrelated to the research in the judgment of the PI, should be reported. The Clinical Director will report these events to the Director, Clinical Center, and to the IC leadership.
3. Unless otherwise specified on the protocol and approved by the IRB, the PI must report all serious adverse events in writing as soon as possible, but within 7 calendar days for death or life-threatening adverse events, and within 15 days for all others to the: i) IRB (which is responsible for reporting to OSHR); ii) IND / IDE sponsor (if pertinent); iii) FDA (if NIH is the sponsor of an IND/IDE); iv) Institutional Biosafety Committee (IBC) and Office of Biotechnology Activities (OBA), NIH (if gene transfer is involved); and v) any other oversight entities specified in the protocol or required by the IC. The Clinical Director should assure that these reporting requirements are met and receive copies of the reports.
4. The PI is responsible for summarizing all adverse events (serious and non-serious, expected and unexpected) as required by the IRB.
5. For adverse event reports presented at continuing reviews, several methodologies, including electronic databases or hard copy forms, may be utilized. The approach to be used in particular protocols should be specified by the PI in the protocol application, endorsed by study monitoring bodies, and approved by the IRB.
6. When reporting an adverse event to the IRB, the PI should address the need and method to communicate pertinent information to research subjects, the need to redesign or amend the research study plans, and whether or not a change in description of risk is warranted in the protocol and the consent form.

Protocol deviations and violations

As noted above, institutions must have procedures for reporting non-compliance. Non-compliance occurs when an investigator fails to comply with federal or state laws or regulations, OHRP or OHSR policy or guidance, or determinations of the NIEHS IRB. Per OHSR policy, investigators are required to promptly report non-compliance to the IRB. The two main types of non-compliance are protocol deviations and protocol violations. A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB. A minor deviation is simply a deviation. A major deviation is known as a protocol violation. A protocol violation is a deviation from the protocol that is likely to affect the subject's welfare and rights, safety, willingness to continue participating in the study, or the integrity or validity of the data. Since a protocol violation may affect the subject's safety, it may also qualify as an unanticipated problem or adverse event (see above). The IRB will decide whether the deviation should be classified as a protocol violation, and how the investigator should respond to the deviation/violation. Examples of protocol violations:

1. A research subject received the wrong treatment or incorrect dose.

2. A research subject met withdrawal criteria during the study but was not withdrawn.
3. A research subject was enrolled but does not meet the protocol's eligibility criteria.
4. Changing the protocol without prior IRB approval.
5. Inadvertent loss of samples or data.
6. Failure to obtain informed consent prior to initiation of study-related procedures
7. Falsifying research or medical records.
8. Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing).
9. Working under an expired professional license or certification
10. Failure to follow federal and/or local regulations, and intramural research.
11. Improper or inadequate consent procedure.
12. Breach of the subject's confidentiality.
13. Conducting research with an expired protocol.

Examples of (possible) minor protocol deviations:

1. Old version of consent form or advertisement used
2. 25 ml of blood accidentally collected when the protocol called for 20 ml blood
3. Accidental needle stick to phlebotomist
4. Data collected at wrong time
5. Patient missed appointment for follow-up
6. Research procedures conducted out of sequence
7. Out-of-date version of consent document used, if no major difference between old and new versions

The only time that investigators are allowed to intentionally deviate from the protocol is when the deviation is necessary to protect the health of a research subject. When this occurs, the investigator must still promptly report the deviation to the IRB. OHRC has a form for reporting protocol deviations. Link to form: [Under development] Contact OHRC for any questions about reporting requirements/procedures.

Other non-compliance

Investigators should report other types of human research non-compliance that they observe to the IRB. For example, if someone at the NIEHS is conducting HSR without an approved protocol, this would be a violation of federal laws and NIH policy, but it would not be an unanticipated problem or protocol deviation because the investigator has no protocol.

Monitoring of human subjects research

HSR at the NIEHS is monitored to protect the rights and welfare of research subjects, and ensure the integrity of the data and compliance with legal and ethical requirements. Sometimes adverse events, unanticipated problems, protocol violations and other types of non-compliance are discovered during the monitoring of HSR, and appropriate reports must be made (see above). Sometimes additional monitoring is necessary to deal with problems and issues that are reported to the IRB. Some monitoring procedures include:

1. Clinical monitoring of research subjects to protect their health and safety;
2. Analysis of data to discern statistical trends relevant to research outcomes and the safety of subjects;
3. Examination of research records, such as data, informed consent documents, brochures, SOPs, and protocols, to ensure compliance with IRB approvals and other legal and ethical requirements;
4. Observation of the informed consent process to ensure that subjects receive the appropriate information, understand the information, are not facing conditions of coercion or undue influence, are capable of making decisions about research participation, and have an opportunity to ask questions.

Not all of these monitoring procedures are appropriate for each study. For example, clinical monitoring is usually only appropriate for more than minimal risk research conducted in a clinical setting. The modes of monitoring include: monitoring by the investigator, monitoring by a data safety monitoring board (DSMB) or independent study monitor, and monitoring by OHRC. As will be discussed below, different modes of monitoring are appropriate for different studies.

From OHSR information Sheet 18:
General - There are four important elements involved in data and safety monitoring:

1. The Principal Investigator (PI) must include a data and safety monitoring plan in each new protocol;
2. The IRB must approve the plan and determine what kind of safety monitoring process (if any) is required: e.g., PI monitoring only; a single independent monitor, or a DSMB;
3. The Institute Clinical Director is responsible for appointing an independent monitor or convening a DSMB (if an applicable Institute DSMB does not already exist - see 4, below);
4. The PI is responsible for providing all required data to the individual monitor or the DSMB and for acting upon any findings made by the DSMB or monitor.

Protocol Monitoring Plan - Principal Investigators (PIs) must address data and safety monitoring by providing a data and safety monitoring plan in all protocols submitted to NIH intramural Institutional Review Boards (IRBs). This plan may be included in the section in the protocol that addresses reporting of adverse events. See Information Sheet #5 "Guidelines for Writing Research Protocols." For many phase I and phase II trials, independent monitors or data and safety monitoring boards (DSMBs) may not be necessary or appropriate, particularly if the protocol involves no more than minimal risk. Continuous, close monitoring by the PI, with prompt reporting of serious adverse events to the IRB (and others, as appropriate) may be adequate. However, at the time of initial review, the PI and the IRB must agree on the appropriate level of monitoring required for the protocol under consideration. Existing protocols without an adverse event reporting/data and safety monitoring section should be amended no later than at the time of IRB continuing review.

Points to consider in deciding what kind of monitoring is appropriate - The IRB should determine what type of monitoring is appropriate for each protocol based on the level of risk and the number of subjects to be studied. Its determination should be recorded in the IRB meeting minutes.

1. Protocols that typically require a DSMB include:
    a. Protocols that generate blinded/randomized data
    b. Multicenter protocols presenting more than minimal risk to subjects

    c. Protocols using gene transfer or gene therapy methodology.
2. Protocols that may require a DSMB or an individual independent monitor include:
    a. Protocols that pose more than minimal risk to the subjects
    b. Protocols that the sponsoring IC believes require special scrutiny because of high public interest or public perception of risk

Institutional Responsibility for DSMBs - Institute Scientific Directors are responsible for providing adequate resources and staff support for any DSMB established by the IC.

Institute Clinical Directors are responsible for appointing members of intramural DSMBs. If a trans-NIH DSMB is needed, appointments will be made by the Associate Director for Clinical Research, NIH.

Some NIH intramural programs (e.g., NCI, NEI and NHLBI) already have Institute- or disease-specific DSMBs to review any protocols that their PIs and the IRB decide need this level of monitoring. Other ICs may also elect to form Institute-specific DSMBs to cover all their eligible protocols or may decide to appoint ad hoc DSMBs either for single studies or for specific conditions/modalities/treatments (e.g., HIV infection or gene transfer). Once an IRB has decided that a protocol requires an independent monitor or DSMB it is the Clinical Director's responsibility either to refer the protocol to an existing DSMB, or to establish an ad hoc DSMB for it.

Intramural protocols may also be subject to monitoring by DSMBs appointed by non-NIH sponsors of multicenter trials. This does not preclude an intramural IC from having the protocol reviewed by an intramural DSMB as well.

Membership of Intramural DSMBs - DSMB members are expected to include clinical trial experts, biostatisticians and physicians and others knowledgeable about the disease/treatment under study. Members should not have professional or financial interests dependent on the outcome of the protocol, and should not be employed by the NIH Institute whose studies are under review, unless otherwise justified and approved by the IC Scientific and Clinical Director.

Responsibilities and Functions of DSMBs and Independent Monitors - Although the responsibilities and functions of DSMBs and independent monitors are not mandated by regulation, their role in protecting the safety of human subjects is critical, and includes:

1. Examining safety and efficacy data and other records from protocols on an explicitly defined schedule
2. Making findings and interpreting data including reporting information to the PI, IRB and IC Clinical Director about continuation, modification, suspension or termination of protocols based on observed beneficial or adverse effects of any of the experimental treatments under study
3. Reviewing the general progress and conduct of the study.

DSMBs generally meet at regular intervals on a schedule that will be determined by the types of protocols being monitored. Additional meetings may also be scheduled when necessary. Intramural DSMBs are

expected to provide findings resulting from each of their meetings to the PI, the IRB and the IC Clinical Director.

Interactions of PIs and NIH IRBs with Intramural DSMBs and Independent Study Monitors - The PI is responsible for providing the DSMB or independent study monitor with any data or other information it requires in order to make its assessments. The PI must report serious, unexpected adverse events and deaths related to the protocol's experimental procedures to the DSMB or independent study monitor at the same time as they are reported to the IRB, the IC Clinical Director and other NIH officials.

IRBs should review DSMB or independent monitor reports as they are received, and not wait to do so until the time of continuing review. They and the PI should act promptly on any findings indicating the need for an amendment to the protocol or affecting the continuation of the protocol. Likewise, PIs and the IRB should notify the DSMB promptly of any protocol amendments they generate.

Monitoring by the Office of Human Research Compliance

In addition to monitoring activities performed by the PI, a DSMB, or an independent monitor, OHRC quality improvement program (QIP) also monitors HSR. Some types of monitoring performed by OHRC include 1) for-cause audits, 2) due diligence review, and 3) routine review.

One of the possible consequences of a possible protocol violation, serious and unexpected adverse event, or serious non-compliance (discussed above) is that a for-cause audit is necessary. A for-cause audit is an audit of research records triggered by a serious issue, such as protocol violation or suspicion of misconduct, and is initiated when the OHRC QIP Coordinator is notified that a serious protocol violation or possible misconduct issue has occurred. The QIP Coordinator will contact the affected site as soon as possible, after the IRB Chair has concluded a preliminary investigation on the infraction. During the audit process, the QIP Coordinator works in conjunction with IRB Administrators and the Director, OHRC, to determine the extent of the violation/misconduct, and to identify any other issues that could impact the safety of human subjects, or the confidentiality of their information. In the course of the audit, the research site's SOPs will be reviewed to ensure that process was followed, and to determine if the process is in compliance with all applicable statutes. Records may be reviewed to assure they are in compliance with federal regulations and institutional policies. The QIP Coordinator may compare the IRB's records to determine accuracy and consistency with the investigator's research records and to verify that the investigator made no material changes to the protocol prior to IRB approval. The QIP Coordinator shares the outcome of the for-cause audit with the principal investigator (PI)/research staff and files a report in the IRB records maintained by the OHRC. As a means of maintaining confidentiality, the QIP Coordinator does not record subjects' protected health information in the findings and notifies the IRB only if the findings reveal significant deficiencies in the protection of human subjects in research. After the audit, the OHRC will send its findings to the research site. The appropriate person at the research site will be asked to develop corrective actions plans based on the audit findings. Audit findings and corrective action plans will be discussed with PI, research staff, OHRC staff and IRB members as applicable to determine if the corrective action plan is appropriate and acceptable. When the IRB receives reports of findings from for-cause audits, the IRB determines whether to report the findings to OHSR, the Food and Drug Administration (FDA), OHRP, or other institutional officials. From time to time, NIEHS may engage in research with other ICs. Should a study that is jointly administered by

NIEHS and another IC be the object of a for-cause audit at a research site, the QIP Coordinator provides the appropriate IC representative with a copy of the resulting audit materials.

Due diligence reviews are an important safeguard, allowing the IRB to have confidence that each site conducting studies understands and enforces the protection of human subjects. A due diligence review is triggered by the submission of a research protocol to the OHRC, involving a research site that NIEHS has not used before. It is initiated when the OHRC QIP Coordinator is notified that a new research site is proposed by a prospective investigator. The QIP Coordinator will contact the new site as soon as possible, to schedule a time for the review. During the review process, the QIP Coordinator works in conjunction with IRB Administrators and the Director, OHRC, to determine an appropriate timeline that will allow the new protocol to begin after IRB approval. In the course of the review, the research site's SOPs will be reviewed to ensure that rules and regulations are understood and followed, and to determine if the process is in compliance with all applicable statutes. The QIP Coordinator may, where applicable, review the IRB membership roster to assure the appropriate composition of the site's IRB, and may request a meeting with the IRB Chair to discuss regulatory issues. The QIP Coordinator shares the outcome of the due-diligence review with the principal investigator (PI)/research staff and files a report in the IRB records maintained by the OHRC. After the review, the OHRC will send its findings to the research site. The appropriate person at the research site will be asked to develop corrective actions plans, if necessary, based on the review findings. Review findings and corrective action plans will be discussed with PI, research staff, OHRC staff and IRB members, as applicable, to determine if the corrective action plan is appropriate and acceptable. When the IRB receives reports of findings from due-diligence reviews, the IRB determines whether to: 1) suspend the enrollment of subjects, if the study has already started, and report the findings to the Office of Human Subjects Research (OHSR), or 2) whether to delay approval of the protocol pending completion of the corrective action plan, if the study has not yet come before the IRB. From time to time, NIEHS may engage in research with other ICs. Should a study that is jointly administered by NIEHS and another IC be the object of a due diligence review at a research site, the QIP Coordinator provides the appropriate IC representative with a copy of the resulting review materials.

Routine reviews are an important safeguard, assuring that OHRC, principal investigators, the NIEHS IRB, and all external research sites are in compliance with all applicable regulations, policies, and procedures governing human subject research. A routine review may occur at any time, and is usually scheduled with reasonable advance notice (usually 4-6 weeks). All routine reviews are initiated by the OHRC QIP Coordinator, in consultation with the Director, OHRC. The types of routine reviews include, but are not limited to, the following:

1. Annual review of OHRC study files, to ensure that all necessary documentation is present
2. Annual review of IRB records, to ensure timeliness of minutes and continuing review, and completeness of documentation
3. Periodic, but at least annual review of investigator complaints and compliments, looking for patterns of problems, and to capitalize on successes
4. Periodic review of contractors and research sites, similar to those conducted for due diligence review
5. Periodic review of the OHRC web site to ensure that all forms are up-to-date, that all links work, and that content is current.

During the review process, the QIP Coordinator works in conjunction with IRB Administrators and the Director, OHRC, to determine that reviews do not interfere with the IRB process, or the workload of the OHRC. The QIP Coordinator shares the outcome of the routine review with the Director, OHRC, and files a report in the QIP records, and in IRB and OHRC study files where applicable. The Director, OHRC, instructs the appropriate person to develop corrective actions plans, if necessary, based on the review findings. Review findings and corrective action plans will be discussed, as appropriate, with PI, research staff, OHRC staff and IRB members, to determine if the corrective action plan is appropriate and acceptable. Where necessary, the IRB receives reports of findings from routine reviews, and processes them under the guidelines established for due diligence reviews.

Informed Consent Guidance

Obtaining the informed consent of the research subject or the subject's representative is one of the most important ethical principles of HSR, and it is also legal requirement. 45 CFR 46 has specific requirements for obtaining and documenting consent, and OHSR and OHRP have developed some useful guidance.

General requirements for informed consent (based on NC and federal law)

1. The subject must have adequate decision-making capacity (DMC). If the subjects lacks adequate DMC, and legally authorized representative (LAR) may provide consent.
2. Consent discussions must take place in a language that is understandable to the subject/representative. Technical terms must be explained in lay language. Reading level of consent documents should be appropriate for the study population (usually 8th grade or less). Appropriate steps must be taken to address the needs of non-English speakers, or people who are deaf or blind (see below).
3. The subject/representative must be given the information that a reasonable person would need to make a decision, under the circumstances. (For specific required information, see below.)
4. The subject/representative's choice should be free from coercion or undue influence, including the undue influence from factors such as money or employment status (for additional information, see below).
5. The subject/representative should not waive or appear to waive any legal rights or release the investigator, institution or its agents from legal liability.

North Carolina law on informed consent in medicine (from NC Statutes 90-21.13)

Informed consent to health care treatment or procedure.

1. No recovery shall be allowed against any health care provider upon the grounds that the health care treatment was rendered without the informed consent of the patient or other person authorized to give consent for the patient where:
    a. The action of the health care provider in obtaining the consent of the patient or other person authorized to give consent for the patient was in accordance with the standards of practice among members of the same health care profession with similar training and experience situated in the same or similar communities; and
    b. A reasonable person, from the information provided by the health care provider under the circumstances, would have a general understanding of the procedures or treatments and of the usual and most frequent risks and hazards inherent in the proposed procedures or treatments which are recognized and followed by other health care providers engaged in the same field of practice in the same or similar communities; or

c. A reasonable person, under all the surrounding circumstances, would have undergone such treatment or procedure had he been advised by the health care provider in accordance with the provisions of subdivisions (1) and (2) of this subsection.

2. A consent which is evidenced in writing and which meets the foregoing standards, and which is signed by the patient or other authorized person, shall be presumed to be a valid consent. This presumption, however, may be subject to rebuttal only upon proof that such consent was obtained by fraud, deception or misrepresentation of a material fact. A consent that meets the foregoing standards, that is given by a patient, or other authorized person, who under all the surrounding circumstances has capacity to make and communicate health care decisions, is a valid consent.

Legally authorized representative (from 45 CFR 46.102(c)

A legally authorized representative (LAR) is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

1. For research involving adults who are unable to provide their own consent, permission for research participation must be obtained from an LAR.
2. Individuals designated as durable power of attorney for health care via…a valid advance directive, or court appointed guardians are acceptable as LARs.
3. Investigators are responsible for informing the LAR about the research as well as assessing his or her understanding and voluntariness as described in this policy.
4. Subjects deemed to be unable to provide their own consent will be so informed.

North Carolina law relevant to legally authorized representatives (NC Statutes 90-21.13)

The following persons, in the order indicated, are authorized to consent to medical treatment on behalf of a patient who is comatose or otherwise lacks capacity to make or communicate health care decisions:

1. A guardian of the patient's person, or a general guardian with powers over the patient's person, appointed by a court of competent jurisdiction pursuant to Article 5 of Chapter 35A of the General Statutes; provided that, if the patient has a health care agent appointed pursuant to a valid health care power of attorney, the health care agent shall have the right to exercise the authority to the extent granted in the health care power of attorney and to the extent provided in G.S. 32A□19(b) unless the Clerk has suspended the authority of that health care agent in accordance with G.S. 35A□1208(a);
2. A health care agent appointed pursuant to a valid health care power of attorney, to the extent of the authority granted;
3. An attorney-in-fact, with powers to make health care decisions for the patient, appointed by the patient pursuant to Article 1 or Article 2 of Chapter 32A of the General Statutes, to the extent of the authority granted;
4. The patient's spouse;
5. A majority of the patient's reasonably available parents and children who are at least 18 years of age;

6. A majority of the patient's reasonably available siblings who are at least 18 years of age; or
7. An individual who has an established relationship with the patient, who is acting in good faith on behalf of the patient, and who can reliably convey the patient's wishes.

If none of the persons listed above is reasonably available, then the patient's attending physician, in the attending physician's discretion, may provide health care treatment without the consent of the patient or other person authorized to consent for the patient if there is confirmation by a physician other than the patient's attending physician of the patient's condition and the necessity for treatment; provided, however, that confirmation of the patient's condition and the necessity for treatment are not required if the delay in obtaining the confirmation would endanger the life or seriously worsen the condition of the patient.

No action may be maintained against any health care provider upon any guarantee, warranty or assurance as to the result of any medical, surgical or diagnostic procedure or treatment unless the guarantee, warranty or assurance, or some note or memorandum thereof, shall be in writing and signed by the provider or by some other person authorized to act for or on behalf of such provider.

North Carolina law—minors

From NC Statutes 48A: A minor is any person who has not reached the age of 18 years.

Specific requirements for informed consent to research

From 45 CFR 46.116:
Basic elements of informed consent:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of informed consent:

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study.

Exceptions/alterations of consent to research

From 45 CFR 46.116:
An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration;

---or---

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Documentation of informed consent

From 45 CFR 46.117:
Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form…The consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent…This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or
2. A short form written consent document stating that the elements of informed consent…have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

Guidance on using the short form

From OHSR SOPs:
In certain circumstances (e.g., illiterate research subjects, blind research subjects), an IRB may approve an oral consent process. This process requires that the IRB review and approve a written summary of what the PI (or person authorized to obtain consent) will say to the subject or his/her legally authorized representative. The summary must be signed by the person obtaining consent and a witness to the oral presentation, and a short written consent form stating that the required elements of consent…were presented orally to the subject by the PI (or his designate). This short written consent form must be signed by the subject and a witness who observed the presentation of information. In the case of illiterate subjects, "making their mark" is adequate…Whenever possible, information in these documents should be provided to the subject or authorized representative in the way that she/he can review and understand (e.g., a tape recording, a Braille document)

Sample consent form

Consent to Participate in Research
Study Title: Name
Principal investigator: Name, affiliation, phone number, email
Associate investigators:
Sponsoring institutions:
Consent document version/date:
Introduction

You are being asked to participate in a research study sponsored by the National Institute of Environmental Health Sciences (NIEHS), which is part of the National Institutes of Health (NIEHS). This study has been approved by an ethics committee at the NIEHS known as an Institutional Review Board (IRB).

Your participation is voluntary. Your decision whether or not to participate in this study will have no affect on any benefits to which you may be entitled or your relationship to the NIEHS. If you decide to participate in this study, you may still withdraw from this study at any time for any reason.

This document contains information about the research study you have been asked to participate in. It is important that you understand this information so that you can make an informed choice whether or not to participate in this study. Please ask questions if there is anything you do not understand.

What is the purpose of this study?
The purpose of study (study name) is to learn more about (disease, condition, phenomenon). In lay language, describe the objectives/goals of the study.

Who can take part in this study?
To take part in this study you must be (state inclusion criteria in lay language). You must not take part in this study if (state exclusion criteria in lay language.) This study will include (state enrollment target) subjects.

What does this study involve?
Participants in the study will be asked to: (Briefly explain the procedures, tests, tasks, interventions, therapies, etc. in lay terms, indicating how long they will last and when they will take place. If appropriate, discuss whether the study will involve randomization, blinding, placebos, investigational drugs or devices. Also state the total length of participation in this study. You may use a chart or table to help organize all this information for the subject.)

What are the benefits of this study?
You may not benefit from being in this study but the knowledge obtained from this study may benefit other people with your (disease or condition).

What are the risks of this study?
The risks of this study include (describe risks associated with each research procedure, test, tasks, etc. Make sure to discuss physical risks (such as bleeding or discomfort), psychological risks (such as stress), and, if appropriate, social, financial or legal risks.)

In addition, with any research study there is a small risk of loss of confidentiality, but we will take measures to minimize this risk and prevent people from discovering your private information.

What are the alternatives to participating in this study?

If this study is evaluating a treatment or other intervention, describe other standard interventions that are available. If the study is not evaluating a treatment or intervention, say, "The alternative to participating in this study is to not participate."

What are the costs of this study?
Describe any costs the subjects must bear, such as payment for tests or procedures. If there are medical procedures, make sure to indicate whether the subject or their insurance company will be billed. If there are no costs, say so. Suggested wording: "There are no costs to participate in this study. You will not have to pay for any of the tests, procedures, or therapies associated with this study."

Will I receive any compensation for being in this study?
Describe any payments subjects will receive for participating in the study, including compensation for travel. Describe when payments will occur and if they will be pro-rated for those who withdraw from the study before completion. Also describe any gifts or other compensation.

What should I do if am injured as a result of participating in this study? (for research classified as more than minimal risk)
If you think that you have been injured as a result of participating in this study, please contact (investigator name, phone, email) as soon as possible. He (or she) will record your information and help you to find medical treatment, if you need it. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIEHS, the NIH, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

How will my confidentiality be protected?
This confidentiality of the information you provide for this study will be protected to the greatest extent allowable by law. We will take the following steps to protect your confidentiality. (Describe procedures, such as limiting access to data or samples, keeping the data in a secured place, etc.). If we report information about you in scientific presentations or publications, we will not use your name. Officials at the NIEHS, NIH, or other government agencies have the right to review research records to ensure the quality and integrity of the data and to protect research subjects from harm.

Will I receive the results of this study?
You will not receive the results from any tests or procedure conducted during this study unless the results may have an impact on your health or your decision to continue participating in this study. You will be informed of new research findings from other studies that may affect your decision to continue participating in this study.

May I withdraw from the study?
You may withdraw from this study at any time for any reason. If you have provided any blood, tissue, or other biological samples for this study, you have the right to withdraw those samples as well. However, data derived from the samples may still be used in this study or future research. To withdraw from this study, please contact (name, phone, email). Additionally, the investigators may withdraw you from the study to ensure the quality or integrity of the data or protect you from harm.

Whom can I contact with questions?
If you have any questions about this study, please contact (investigators name, phone, email). If you have any questions about your rights as a research subject, please contact the NIEHS Office of Human Research Compliance at: (919) 541-4265

Consent to participate in this study
I have read and understood information about (name of study), I have had the opportunity to ask questions about it, and I have received a copy of this document for my records. I agree to participate in this study.

_____

Participant's signature (or legal representative) printed name date

_____

Investigator signature (or designee) printed name date

If the research involves a minor, age 7-17, add:

_____Assent of minor

printed name date

The IRB may also require a document for the minor to read (a shorter and simpler version of the consent document)

Sample short form (from OHSR SOPs)

Consent to Participate in a Research Study

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Before you decide whether or not to participate, the researcher will tell you about:

1. The purposes of the research;
2. How much of your time the research will take;
3. What research procedures you will undergo;
4. The risks to you of taking part in the research;
5. Any benefits of the research to you or to other people;
6. How your confidentiality will be protected; and
7. What other options you may have instead of taking part in this research.

Other Pertinent Information

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance. The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.
2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.
3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.
4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator,

Building: , Room , Telephone: .You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

_____

Signature of Research Participant/ Date

_____

Signature of Witness/Date

Language to use for HIV testing/consent as part of a research study

From OHSR SOPs (can be modified for NC/NIEHS context):
As part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 teaspoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small risk of you fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

1. Your physician will notify you promptly of the HIV test results.
2. Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.
3. Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.
4. The results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.
    a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.

b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.
c. The Clinical Center may report certain communicable diseases, including AIDS and symptomatic HIV infection, to appropriate State and Federal government agencies.
    1) For Clinical Center patients who are Maryland residents, the Clinical Center reports by "Patient Unique Identifier Number" (rather than by name) newly obtained HIV-positive results from its laboratory to the Maryland Department of Health and Mental Hygiene. Patient Unique Identifier Number is: last four digits of social security number, birth month, birth day, birth year, race and gender.
    2) For Clinical Center patients who are Maryland residents, the Clinical Center reports by name new cases of AIDS to the Maryland Department of Health and Mental Hygiene.
    3) For Clinical Center patients who are not Maryland residents, the Clinical Center reports HIV-positive results and/or AIDS to the patient's primary care/referring physician

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor: [phone #].

Enrolling non-English speaking subjects in research

From OHSR SOPs:
Expected enrollment of non-English speaking subjects: In some protocols, the PI expects non-English speaking subjects to enroll because, for example, the protocol is studying a disease or condition that is likely to attract them or the PI is actively recruiting them. When the study subject population includes non-English speaking people or the PI and/or the IRB anticipates that consent discussions will be conducted in a language other than English, the IRB shall require a translated consent document to be prepared. In order to assure itself that the translation is accurate, the IRB may choose to have a back translation or review of the document by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they are given a copy of the translated consent document. [Subjects and witnesses sign the translated document.]

Unexpected enrollment of a non-English speaking subject: If a non-English speaking subject is unexpectedly eligible for protocol enrollment, there may not be an extant IRB-approved written translation of the consent document. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must receive IRB approval to follow the procedures for oral informed consent. The English version of the informed consent document may be used as the written summary (see Attachment 5-6). The CC standard short written consent form translated into the most common languages used in the CC may be obtained by contacting Protocol Services or on

the CC web site under “Staff Information” (for translations and back translations, see “Short Written Consent Forms for English and Non-English Speaking Research Subjects”). For all other languages, the PI is responsible for obtaining translation(s) of the short written consent form. Translation of the short written consent form may be obtained by contacting OHSR.

Use of interpreters in the consent process: Unless the PI is fluent in the prospective subject’s language, an interpreter will be necessary to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) shall assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible). The interpreter may sign the consent document as the witness and should note “Interpreter” under the signature line. The PI (or authorized person) must document this process in the progress notes of the subject's medical record, including the name of the interpreter.

Payments to research subjects

From OHSR information sheet 20:
This information on remuneration of research subjects will assist investigators in writing/designing studies and consent documents that involve remuneration and assist IRBs in reviewing/approving them. This information will help to guide judgments about the appropriateness of remuneration. Such a judgment takes into consideration the recruitment needs, the expected benefits to individuals, and the vulnerabilities of the potential subjects for each clinical protocol. In addition, guidance provided here may promote standardization and consistency in the practice of remunerating subjects, while permitting flexibility and the consideration of practicalities.

ETHICAL CONSIDERATIONS REGARDING REMUNERATION OF RESEARCH SUBJECTS
Remuneration to research subjects may be justified on at least four distinct grounds,

1. As reimbursement for expenses,
2. A means to reduce financial sacrifice on the part of the subjects,
3. Compensation for their time and effort, or
4. An incentive to facilitate adequate and timely recruitment for and/or completion of a study.

Although paying subjects is common and pervasive and has been done for many years, there remains some discomfort with the practice. Moral concerns include:

1. The possibility that paying subjects may be an ‘undue inducement’, that is, inducing people to participate in research against their interests;
2. The potential that an offer of money may obscure the risks of research and/or provide an incentive to conceal relevant information, and
3. The possibility that payment preferentially attracts poorer populations as research participants.

These concerns relate to paying any research subject, whether they are patient or healthy volunteers. A successful approach would balance these concerns with the reasons for offering remuneration.

To what extent should patient-subjects be treated differently from healthy subjects, especially with respect to the above concerns? Some argue that since patient-subjects are more likely to receive benefit from participating in research, they should not be paid. However, many studies offer no direct benefit to patient subjects. While payment may be unnecessary as a recruitment incentive for studies that do offer possible therapeutic benefit, there is nothing inherently wrong with offering payment to patient-subjects in these studies. Some people object to paying patients because they see patients as more vulnerable than healthy subjects and therefore in need of greater protections. Vulnerability is based, presumably at least in part, on a patient's dependency on their physician and on the possibility that patients will perceive participation in research as treatment designed to benefit them ('therapeutic misconception'). Offering remuneration to patient subjects may, in fact, reduce the therapeutic misconception by clarifying for them what is done for their benefit and what is done for research purposes only.

POLICY AND COMMUNICATIONS BULLETIN, THE CLINICAL CENTER
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SUBJECT: Reimbursement of Travel and Subsistence Expenses for NIH Clinical Research Protocol Participants

PURPOSE: This chapter establishes a policy for reimbursement of travel and subsistence expenses for participants in clinical research protocols at all NIH intramural clinical research sites.

GUIDING PRINCIPLES: NIH will make every effort to assure fairness in reimbursing clinical research protocol participants for travel and subsistence by taking into account the scientific needs of the studies and the financial and/or medical needs of individual participants.

No U.S. citizen or permanent U.S. resident residing in the U.S. who otherwise meets eligibility requirements will be denied enrollment in clinical research protocols because of their inability to pay the costs of travel and subsistence.

POLICY: This policy establishes the requirement for each protocol to establish a protocol-specific reimbursement rate for travel (i.e., local and long-distance transportation) and subsistence (i.e., meals and lodging) ranging from zero up to the government rate. Participants will be made aware of the protocol-specific reimbursement rate as part of the enrollment process. Each participant will be provided reimbursement at the specified rate upon request.

Participants needing additional financial assistance will be able to receive supplemental reimbursement based upon need. Requests for supplemental reimbursement will be evaluated on a case-by-case basis for valid financial and/or medical need through a standardized process.

In establishing the travel and subsistence reimbursement rates for a protocol, Principal Investigators (PIs) must consider a set of objective factors, including reimbursement practices of similar protocols at the NIH, the rarity of the disease being studied, the benefit/burden being placed on the subject and family,

and special needs of the participants. These factors will be used by the Institute Clinical Directors in approving the reimbursement rates to assure that proposed reimbursement practices are equitable.

In setting reimbursement levels for lodging, protocols must specify whether they will authorize use of The Children's Inn and The Edmond J. Safra Family Lodge. If use of these lodging facilities is authorized, full reimbursement at the current nightly rates will be required.

SCOPE: This policy applies to U.S. citizens or permanent U.S. residents residing in the U.S. (and parent/guardian for pediatric protocol participants or authorized attendant for adults) enrolling in research protocols that take place at NIH intramural clinical research sites, including protocols located on the NIH campus in Bethesda, Maryland, and at all other NIH intramural locations.

For participants whose home of record is outside the U.S., travel expenses from a U.S. port of entry may be covered.

The specific procedures for implementation will vary by site; however, all applicable travel guidelines outlined in the procedures section of this policy must be followed.

This policy does not address the issue of compensation that may be offered under a protocol other than reimbursement for travel and subsistence for participants.

DEFINITIONS:
Protocol-Specific Reimbursement Rate: Amount of financial coverage provided to clinical research protocol participants (and parent/guardian for pediatric protocol participants or authorized attendant for adults) for travel and subsistence by the sponsoring Institute or Center (IC). This rate can range from zero up to the government rate. The parameters of coverage are detailed below (see “Parameters of Coverage”).

Supplemental Reimbursement: Additional financial assistance, above the protocol-specific reimbursement rate, made available by Institutes to clinical research protocol participants with valid financial and/or medical need. Generally, supplemental reimbursement extends coverage up to the full government rate; the amount is at the discretion of the IC and the ICs may authorize supplemental reimbursement above the full government rate on an as-needed basis (e.g., a participant may require two airline seats for medical necessity).

Travel: Transportation of a person by car, bus, train or plane; refers to both local and long-distance. The parameters of coverage are detailed below (see “Parameters of Coverage”).

Subsistence: Refers to meals and lodging. The parameters of coverage are detailed below (see “Parameters of Coverage”).

PARAMETERS OF COVERAGE: The mode of travel approved will be the least expensive unless otherwise authorized.

NIH will pay for expenses that involve travel from the home of record to the NIH site. Unless medically indicated, NIH will not pay for expenses that involve alternate routes. Unnecessary stops or delays along the way for sight-seeing, visits, vacations, or to increase frequent flyer miles will not be authorized, even if it makes the travel less expensive.

NIH will not pay for expenses that are incurred beyond the approved time period of the visit.

Local Travel: Protocol participants who live within 50 miles of the NIH clinical research site are eligible for reimbursement of local travel at the protocol-specific reimbursement rate. The approved modes of local travel are as follows:

1. Car: The government will reimburse participants for car mileage. Reimbursement for rental cars will not be allowed beyond the car mileage reimbursement rate.
2. Taxi/Train/Bus: Participants traveling by taxi, train, or bus will be reimbursed if authorized.

Long-Distance Travel: Protocol participants who live more than 50 miles of the NIH clinical research site are eligible for reimbursement for long-distance travel at the protocol-specific reimbursement rate. The approved modes of long-distance travel are as follows:

1. Air: The government will pay for air transportation from the airport nearest to the home of record to the least expensive airport near the NIH clinical research site.
2. Train: The government will pay for train tickets.
3. Car: The government will pay for car mileage provided the cost of the round trip does not exceed a round trip government-rate airline ticket. Reimbursement for rental cars will not be allowed beyond the car mileage reimbursement rate.
4. Bus: The government will pay for bus tickets provided the cost of the round trip does not exceed a round trip government-rate airline ticket.

Lodging: Participants will be provided reimbursement for lodging expenses in accordance with the protocol-specific reimbursement rate for participants living greater than 50 miles from the NIH clinical research site. If the hotel cost is less than the protocol-specific reimbursement rate, NIH will only reimburse for the actual cost of the lodging.

Meals: Protocol participants who live greater than 50 miles from the NIH clinical research site are eligible for reimbursement in accordance with the protocol-specific reimbursement rate for meals at a daily rate.

PROCEDURES

1. Establishing the protocol-specific reimbursement rate. During the development of a new protocol or at the time of renewal for existing protocols, the PI will complete the "Designation of Reimbursement of Travel and Subsistence (DRTS) Expenses for NIH Intramural Clinical Research Protocols" (Form NIH 2868). In completing the DRTS form, the PI will consider the disease characteristics, benefit/burden to participants, scientific need and the reimbursement practices of similar protocols

and will determine a protocol-specific reimbursement rate for travel and subsistence expenses. The protocol reimbursement rate can range from zero up to the government rate.

The DRTS form (Appendix A) can be accessed from the CC Office of Protocol Services (301-496-0744) at http://intranet.cc.nih.gov/ops/ and at http://intranet.cc.nih.gov/patienttravel. Investigators can query protocols to identify protocols with similar disease characteristics identified on the DRTS Form, as well as by reimbursement, protocol number, or PI at:
http://intranet.cc.nih.gov/ops/pdf/DTRS.pdf

The PI or designee and the CC Office of Protocol Services will ensure that each protocol consent document (upon establishment or at the time of annual review if the protocol is still actively accruing participants) includes the following statement:
"Reimbursement of travel and subsistence will be offered consistent with NIH guidelines."

The PI will sign the completed DRTS form and submit it to the Clinical Director as a part of the protocol package.

2. Approving the protocol-specific reimbursement rate. The IC Clinical Director will ensure that the protocol review package includes a completed DRTS form and a new consent document as referenced in Section 1.

   The IC Clinical Director will review the DRTS form as part of the protocol review package to ensure that the PI has considered the relevant factors in establishing the protocol-specific reimbursement rate.

   The protocol-specific reimbursement rates will be considered effective as of the date of the final IRB approval of the complete protocol package.

3. Informing participant of the policy, protocol-specific reimbursement rate and reimbursement options. The PI or designee will inform prospective and current protocol participants of the policy on Reimbursement of Travel and Subsistence Expenses for NIH Clinical Research Protocol Participants and the protocol-specific reimbursement rate (for air/rail travel, car mileage, meals and lodging). The PI or designee may opt to send written documentation to prospective and current protocol participants describing this policy and the protocol-specific reimbursement rate. A sample generic notification memorandum is available at http://intranet.cc.nih.gov/patienttravel.

   The PI or designated IC research coordinator will explain the three reimbursement options to the participant and will ask the participant to select one:

   a. Accept protocol-specific reimbursement
   b. Decline reimbursement
   c. Request supplemental reimbursement for financial or medical need

4. Entering the reimbursement option selected by participant. Once a reimbursement option is selected by a protocol participant, the PI or designated IC research coordinator will document the participant's selection in the Admissions/Travel/Voucher (ATV) system. If applicable, the PI or designated IC research coordinator will initiate a request for a financial or medical needs assessment in the ATV system which generates a service request to the CC Social Worker or the CC Patient Travel Coordinator respectively.

5. Explaining travel planning steps to participant. The PI or designee will explain the travel planning steps that correspond with the selected reimbursement option:

    a. Participant ACCEPTS protocol-specific reimbursement
        1) If the protocol-specific reimbursement rate is set at (or above) the government rate for air/rail travel. The PI or designee will direct the participant to contact the Patient Travel Office to have air or rail travel arranged and paid by the government. The PI or designee will instruct the participant to arrange and pay for his/her own lodging. The PI or designee will inform the participant to keep receipts for reimbursement of lodging and other travel expenses.
        2) If the protocol-specific reimbursement rate is set below the government rate for air/rail travel. The PI or designee will instruct the participant to arrange his/her own air or rail travel and lodging at his/her own expense. The PI or designee will inform the participant to keep receipts for reimbursement of these and other travel expenses. The participant may contact the Patient Travel Office for assistance with air/rail travel planning.
    b. Participant DECLINES reimbursement. The PI or designee will inform the participant to arrange ALL travel and lodging at his/her own expense. The participant may contact the Patient Travel Office for assistance with air/rail travel planning.
    c. Participant REQUESTS supplemental reimbursement
        1) If the request is for financial need. The PI or designee will inform the participant that he/she will be contacted by the CC Social Worker who will conduct an in-person or phone interview to evaluate financial need using a standardized assessment tool that was developed by the Social Work Department. Within three days of the interview, the CC Social Worker will evaluate the participant's responses and record the results of financial assessment in the ATV system. The PI or designee will check the results of the financial assessment in the ATV system and inform the participant of the decision.

            If the participant is approved for supplemental reimbursement, the PI or designee will then instruct the participant to follow the appropriate travel planning steps from Section 5a. If participant is denied supplemental reimbursement but accepts instead the protocol-specific reimbursement rate, the PI or designee will then instruct the participant to follow the appropriate travel planning steps from Section 5a.

        2) If the request is for medical need. The PI or designee will determine if supplemental reimbursement for medical need should be provided to the participant. This determination is based on individual participant need and the scientific/recruitment needs of the protocol. As a management control, the CC Patient Travel Coordinator will review supplemental reimbursements for medical necessity to ensure that patient travel funds are the appropriate

funding mechanism to cover the request. If patient travel funds are not the correct funding source, the CC Patient Travel Coordinator will contact the PI or designee to determine alternative resources. The PI or designee will specify the supplemental reimbursement amount in the ATV system and inform the participant of the decision.

If the participant is approved for supplemental reimbursement, the PI or designee will then instruct the participant to follow the appropriate travel planning steps from Section 5a. If participant is denied supplemental reimbursement but accepts instead the protocol-specific reimbursement rate, the PI or designee will then instruct the participant to follow the appropriate travel planning steps from Section 5a.

6. Explaining the reimbursement process to participant. The PI or designee will explain the following information to participants who pay up-front for travel, lodging and/or meal expenses that have been approved for reimbursement:
   a. The participant can receive a travel voucher for reimbursement of approved travel-related expenses from the CC Voucher Office.
      1) Hours of Operation: Monday – Friday 8:30 am – 5:00 pm
      2) Proof of payment (receipts) is required for lodging and travel expenses (not required for meals or mileage)
   b. The CC Voucher Office will prepare a voucher in accordance with the protocol-specific reimbursement or supplemental reimbursement rate for the dates authorized on the ATV request.
   c. The participant has two options for receipt of payment:
      1) Obtain voucher from the CC Voucher Office and take it to the NIH Cashier's Office and receive cash or a check (picture identification is required to receive funds).
      2) Request at the CC Voucher Office to have the reimbursement check mailed to participant's home of record.

SUMMARY OF RESPONSIBILITIES

1. The Medical Executive Committee, in conjunction with the CC Director, will:
   a. Conduct an annual assessment of the policy, including but not limited to, policy compliance; IC-specific and overall NIH expenditures on patient travel; and any unforeseen administrative or patient-associated impacts related to the process.
   b. Provide the Deputy Director for Intramural Research an annual summary of above assessment.
2. The Principal Investigator (PI) will:
   a. Complete, sign and submit a "Designation of Reimbursement of Travel and Subsistence (DRTS) Expense for NIH Intramural Clinical Research Protocols" (Form NIH 2868) to the IC Clinical Director along with every protocol review package.
   b. Inform prospective and current protocol participants of the policy on Reimbursement for Travel and Subsistence Expenses for NIH Clinical Research Protocol Participants and the protocol-specific reimbursement rate.
   c. Ensure that each protocol consent document includes the following statement: "Reimbursement for travel and subsistence will be offered consistent with NIH guidelines."

3. The Institute Clinical Directors (CD) will:
    a. Ensure that their Institute is in compliance with this policy.
    b. Monitor quarterly reports from the Clinical Center of their Institute's expenditures on patient travel.
    c. Ensure that the protocol review package includes a completed DRTS form.
    d. Review the DRTS form as part of the protocol review package to ensure that the PI has considered the relevant factors in establishing the protocol-specific reimbursement rate.
4. The Institutes' or Centers' (IC) research coordinators will:
    a. Communicate this policy and protocol-specific reimbursement rates to new and existing clinical research protocol participants and provide instructions to participants.
    b. Notify the CC Patient Travel Coordinator of any participant or IC concerns and/or issues.
    c. Serve as a liaison between participants, the CC Patient Travel Coordinator, the CC Admissions Office, the CC Voucher Office and other stakeholders.
    d. Generate participant travel requests in the Admission Travel Voucher (ATV) system.
5. The Clinical Center will:
    a. Serve as the primary point of contact for resolution of any participant or IC concerns and/or issues related to travel.
    b. Evaluate requests for supplemental reimbursement.
    c. Assist with training IC research teams.
    d. Serve as a liaison between participants, IC research coordinators, the CC Admissions Office, the CC Voucher Office and other stakeholders.
    e. Provide ICs with quarterly summary reports of IC expenditures on patient travel (by CAN and protocol).
    f. Maintain a website that permits investigators to query protocols by disease characteristics, reimbursement amount, protocol number, or PI.
    g. Will process vouchers for participant reimbursement.
    6. The NIH Cashier's Office will provide cash or checks to protocol participants.

REFERENCES:

The "Designation of Reimbursement of Travel and Subsistence (DRTS) Expense for NIH Intramural Clinical Research Protocols" (Form NIH 2868) can be accessed from the CC Office of Protocol Services (301-496-0744) at http://intranet.cc.nih.gov/ops/ and at http://intranet.cc.nih.gov/patienttravel.

Investigators can query protocols to identify protocols with similar disease characteristics identified on the DRTS Form, as well as by reimbursement, protocol number, or PI at http://pqs.cc.nih.gov/protocol_query/pi_institute_search.

Government Travel Rates

1. Government rates for round trip airfare are available at http://www.gsa.gov/citypairsearch
2. Government rate for car mileage is available at http://www.gsa.gov/mileage
3. Government rate for meals is available at http://www.gsa.gov/perdiem (Search for DC Metropolitan rate.)

4. Government rate for lodging is available at http://www.gsa.gov/perdiem (Search for DC Metropolitan rate.)

Returning results to research subjects

From OHSR SOPs

In general, one of the expectations human subjects have when they participate in research is that they learn something from their involvement. Principal Investigators (PIs) usually share appropriate research information with the subjects of their studies, either during the course of participation or after the study has been completed. However, the sharing of information with research subjects is not always explicitly addressed in informed consent documents.

In some cases, PIs and IRBs agree that, for various reasons, certain research information, particularly genetic research information, ought not to be shared with research subjects, and occasionally, NIH informed consent documents contain IRB-approved language which states that certain information will not be provided to research subjects. However, the Federal Privacy Act applies to the records of research conducted at the NIH when such records are retrievable by an individual identifier (see attached Summary of the Privacy Act). This means that any language in a consent form that waives an individual's right to obtain access to his/her records is inconsistent with the Privacy Act as well as with the Federal Regulations for the Protection of Human Subjects (45 CFR 46). These regulations prohibit the use of language in informed consent documents that would waive or appear to waive the rights of the subject (45 CFR 46.116).

In order to ensure compliance with the Privacy Act and the Federal regulations, effective immediately, for new protocols where the IRB and the PI agree that it is in research subjects' best interests not to have research information provided to the subjects, informed consent documents must explain the reason for this limitation and not remain silent about it. Also, the consent documents must state explicitly that subjects do not waive any rights they may have regarding access to research information. Current consent documents that restrict subjects' access to research information should be carefully checked by the IRB and PI at the time of continuing review and revised appropriately.

A subcommittee of the Human Subjects Research Advisory Committee (HSRAC), which included the NIH Legal Advisor, has developed the following suggested informed consent language for use in such cases. The first paragraph offers various options (italicized in brackets) for informing subjects that their access to information may be limited. This paragraph may be altered or expanded by the PI and the IRB as necessary to fit the protocol, but the language of the second paragraph must not be changed, although where it is placed in the informed consent document should be as judged appropriate by the PI and the IRB. Furthermore, it is only necessary to include these two paragraphs in consents where subjects' access to research information is to be limited; they are not required if PIs plan to allow subjects unlimited access to information.

> "The investigators conducting this study do not plan to provide you with the results of any medical tests or evaluations or other information pertaining to you, or other research data or

results because [the results will be preliminary] [the results will require further analysis] [the results may reveal unwanted information about family relationships] [further research may be necessary before these results are meaningful]. [If meaningful information is developed from this study that may be important for your health, you will be informed when it becomes available.]

"By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. _____(PI)."

It is important for PIs to know that if a subject requests medical/research information about himself or herself, the Federal Privacy Act requires the PI to give that information either to the subject or to a third party designated by the subject (such as a family physician) whether or not the subject has signed a consent form that contains language similar to that above. The Privacy Act regulations' special access provision applies to medical records, and although there is no definition of "medical," the NIH Legal Advisor considers the term broad enough to encompass records of experimental tests and treatment provided in clinical research. PIs are strongly urged to familiarize themselves with the provisions of the Privacy Act in order to make sure they understand how this act applies to their research.

Guidance for Special Categories of Research

Research involving Children

From OHSR Information Sheet 10:
The mandate of Institutional Review Boards (IRBs) is to protect the rights and safeguard the welfare of human research subjects. Children are considered a vulnerable research population because their physical and intellectual capacities are limited and special ethical and regulatory considerations are involved when investigators design and IRBs review research involving children. Title 45 CFR Part 46, Subpart D provides for "Additional Protections for Children Involved as Subjects of Research" and may be obtained by calling OHSR, 301-402-3444. For Clinical Center policy, see Medical Administrative Policy (MAS) #92-5 (may be obtained by calling 301-496-5939).

In March, 1998, the NIH issued Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. Intended to foster the increased participation of children in research, the Policy and Guidelines mandate that children must be included in all human subjects research conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

DEFINITIONS:
1. Assent means a child's affirmative agreement to participate in research. Failure to object should not be construed as assent.
2. Benefit is a valued or desired outcome.
3. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted. Generally the law considers any person under 18 years old to be a child.
4. Risk is the probability of harm (physical, emotional, social or economic). Both probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only minimal risk.
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. A list of procedures which may be reviewed through an expedited review procedure, if the IRB Chair or his designee consider them minimal risk, are provided in 45 CFR 46.110 and the NIH Standard Operating Procedures for IRBs Attachment 5-8, found on the OHSR website, http://ohsr.od.nih.gov. Also, see Assessing probable risks/discomforts at 3. below.
6. Permission is the agreement of parent(s) or guardian(s) to the participation of their child or ward in research.

INVESTIGATOR AND IRB CONSIDERATIONS: An IRB reviewing research involving children must consider the benefits, risks, and discomforts of the research and assess their justification for children's participation in light of the benefits to the child-subject(s) or to society as a whole. In calculating the risks and benefits, the IRB should consider the circumstances of the subjects under study, the magnitude of

risks or discomforts that may accrue from research participation and the potential benefits the research may provide to the subject or class of subjects.

The Federal regulations permit four categories of research involving children. The categories are determined by the degree of risk and prospect of benefit to the participating child-subject. For any protocol involving children, the IRB, in consultation with the Principal Investigator (PI), is responsible for determining in which of the four categories of research the study belongs and for documenting in the minutes the rationale for its choice. Therefore, it is desirable for the PI to address these issues directly in the protocol in a section entitled “The ethical and regulatory considerations concerning the involvement of children” in which he/she identifies which of the categories the study fits into and the rationale for this categorization.

The four categories of research which may be approved by IRBs are:

1. Category 1: research that does not involve greater than minimal risk to children (see Assessing probable risks/discomforts, below).
2. Category 2: research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child-subject.
3. Category 3: research involving greater than minimal risk and no prospect of benefit to the individual child-subject. In order to approve research in this category, an IRB must determine that the risk of the research represents no more than a minor increase over minimal risk; that the intervention or procedure presents experiences to the child-subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; and the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition.
4. Category 4: research not otherwise approvable under one of the above categories but the IRB determines that the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. In these cases the IRB will forward the research for review by the Deputy Director for Intramural Research (DDIR). If he/she agrees, the study will be forwarded to the Secretary of HHS who may approve the research after consultation with a panel of experts. The panel must determine that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and that the research will be conducted in accordance with sound ethical principles.

In all cases, the IRB must determine that adequate provisions have been made for soliciting permission of the parents or legal guardians and the assent of the children.

Assessing probable risks/discomforts: An important aspect of IRBs' considerations of research involving children is an evaluation of what constitutes “minimal risk.” Procedures which generally present no more than minimal risk to healthy children include: urinalyses, small amounts of blood obtained by venipuncture, electroencephalography (EEG), allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However, the assessment of the probability

and magnitude of harm or discomfort may be different in sick children and may vary depending on the diseases or conditions that the children may have. For example, obtaining research blood samples from a very ill and anemic child may present more than minimal risk to the child. On the other hand, an IRB may consider that children suffering from chronic illnesses who are accustomed to invasive procedures are placed at minimal risk by involvement in similar research procedures, in contrast to children who have not had such experiences. The IRB must also consider the extent to which research procedures would be a burden to a child-subject, regardless of whether the child is accustomed to the proposed procedures.

Procedures that exceed minimal risk may be difficult to define in the abstract, but should not be difficult to identify on a case-by-case basis. Higher risk procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress also may exceed minimal risk.

Assessing possible benefits: In assessing the possible benefits of research participation, the IRB should consider the variability in health status of potential subjects. For example, a potential subject might be a normal, healthy child, or a child who has been exposed to a disease or toxin (e.g., chicken pox, lead) where it is known that a percentage of the children exposed will experience untoward consequences. A child might be in the early stages of disease (e.g., HIV infection) or may suffer from the disease or other significant medical or psychiatric disorders. Thus the IRB must take into account the current health status of the child-subjects and the likelihood of progression to a worsened state without research intervention.

PERMISSION AND ASSENT: When children or minors are involved in research, IRBs are required to make provisions for the assent of the children and the permission of the parents.

Because children have not reached their full intellectual and emotional capacities and are unable to give legally valid informed consent, involving them in research requires the permission of their parents or legal guardians. The IRB must determine whether the permission of both parents is required. However, in some cases, such as child abuse or treatment of venereal disease, parental permission may not be appropriate.

Although children are not capable of giving legally valid consent, they may be able to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether or not they wish to participate in research, particularly if they can comprehend and appreciate what it means to be a volunteer for the benefit of others and the research is not likely to benefit them directly. Taking into account such factors as the nature of the research, and the age, status and medical condition of potential subjects, the IRB must determine for each protocol, whether all or some of the children are capable of assenting to participation. There is no requirement that assent be sought at a specific age, but that it be sought when in the judgment of the IRB, the children are capable of providing assent.

REMUNERATION/COMPENSATION: If compensation is to be paid, a section should be included in the consent document to be signed by the parent and in the assent document, if inclusion in the assent document is considered appropriate by the IRB.

WARDS OF THE STATE: When conducting research involving wards of the state, additional requirements may be applicable as discussed in MAS# 92-5 or 45 CFR 46.409.

FOR MORE INFORMATION: A checklist of issues for IRBs to consider in research with children is posted on the NIH Pediatric Staff website at http://www.cc.nih.gov/ccc/pedweb/pedsstaff/index2.html
A list of NIH intramural pediatricians who are available to serve as ad hoc IRB consultants for review of protocols involving children is attached.

Inclusion of women and minorities in research

From OHSR Information Sheet 11:
The principle of Justice as outlined in the Belmont Report requires that research subjects be treated fairly. For example, subjects should be carefully and equitably chosen to insure that certain individuals, or classes of individuals are not systematically selected or excluded, unless there are scientifically or ethically valid reasons for doing so.

Consistent with this principle, the NIH Revitalization Act of 1993 legislated that special attention be given to the inclusion of women and minority groups in all clinical research conducted or supported by the NIH.

On March 9, 1994, the NIH issued Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (copy available from OHSR). These Guidelines focus on the requirement for appropriate representation of women and minority groups in all NIH-supported or -conducted clinical research, particularly in Phase III clinical trials. On August 2, 2000, the NIH updated the Guidelines to reflect the requirement to include in the research plan of Phase III trials a description of how valid analyses will be conducted to detect significant differences in intervention effect among different populations. To review the update, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html. Even though most Intramural Research Program (IRP) clinical research does not consist of Phase III clinical trials, the Guidelines nevertheless direct that all IRP clinical research projects should strive to recruit and enroll the most diverse study population consistent with the purpose of the project.

The Guidelines contain the following policy statements:

“It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute or Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.”

“The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection for such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants.”

NIH Intramural Research Program Principal Investigators (PIs) and Institutional Review Boards (IRBs) implement these Guidelines as follows:

1. Design of protocols: In their clinical research protocols, PIs must include in the protocol's headed section entitled Human Subject Protections:
    a. The rationale for the research subject selection based on a review of the gender and population category(ies) at risk for the disease or condition being studied;
    b. Strategies and procedures for recruiting the subject population selected in (a) above, and
    c. Justification for exclusions, if any, of women and/or individuals from particular population categories.

    A Targeted/Planned Enrollment Table should be included in the protocol for Phase III and IV trials. The format for this table can be found in the NIH Standard Operating Procedures for IRBs, 6-6a. See OHSR website at http://ohsr.od.nih.gov/irb/procedures.html
2. Initial IRB review of protocols: The IRB is required to review and approve the rationale for research subject selection; the strategies and procedures for recruiting subjects, and the justification for exclusion of women and/or individuals from particular population categories. Exclusions may be warranted because of the nature of the disease or condition being studied, or there may be other justifiable reasons.
3. Continuing IRB review of protocols: Continuing review and approval of clinical research protocols by IRBs must include a review of the cumulative number of subjects accrued by gender and ethnic/racial category(ies), provided by the PI on the Inclusion Enrollment Report form. In the course of its continuing reviews of a particular protocol, the IRB may find that the cumulative data on subject enrollment are inconsistent with its previously approved subject selection (see 1. and 2., above). In these cases, the IRB has broad discretion in exercising its judgment on how to proceed. Actions from which it may choose include:
    a. Continuation of subject accrual with referral of the matter to the IC Clinical Director for evaluation of recruitment strategies and additional resources, or
    b. Termination of the protocol for failure to meet the terms and conditions of IRB approval.
4. As with any other protocol submission determined by the IRB to be incomplete, IRBs are expected to defer initial or continuing review of any protocol that does not include items (1), or (3) above, respectively.

A primary aim of clinical research is to provide scientific evidence leading to a change in health policy or a standard of care, and therefore it is imperative to determine whether the experimental intervention or therapy affects women, men or individuals from various racial and ethnic groups differently. The objective is to recruit actively the most diverse study population consistent with the purpose of a research project. At the NIH, this objective is met by the conscientious implementation of the Guidelines by PIs and IRBs.

Pregnant women and fetuses in research

From 45 CFR 46.202-204:
DEFINITIONS:

1. Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
2. Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.
3. Fetus means the product of conception from implantation until delivery.
4. Neonate means a newborn.
5. Nonviable neonate means a neonate after delivery that, although living, is not viable.
6. Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.
7. Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
8. Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the

fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

Research involving neonates

From 45 CFR 46.205:

1. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:
   a. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
   b. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
   c. Individuals engaged in the research will have no part in determining the viability of a neonate.
   d. The requirements of paragraph (b) or (c) of this section have been met as applicable.
2. Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:
   a. The IRB determines that:
      1) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
      2) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
   b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
3. Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:
   a. Vital functions of the neonate will not be artificially maintained;
   b. The research will not terminate the heartbeat or respiration of the neonate;
   c. There will be no added risk to the neonate resulting from the research;
   d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
   e. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).
4. Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

Research involving prisoners

From 45 CFR 46.303-306:
DEFINITIONS: As used in this subpart:

1. Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
2. DHHS means the Department of Health and Human Services.
3. Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
4. Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

1. A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
2. At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

Additional duties of the Institutional Review Boards where prisoners are involved.

1. In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:
    a. The research under review represents one of the categories of research permissible under §46.306(a)(2);
    b. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
    c. The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
    d. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator

provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

e. The information is presented in language which is understandable to the subject population;

f. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

g. Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

2. The Board shall carry out such other duties as may be assigned by the Secretary.

3. The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

Permitted research involving prisoners.

1. Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:
   a. The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; and
   b. In the judgment of the Secretary the proposed research involves solely the following:
      1) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
      2) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
      3) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
      4) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.
2. Except as provided in paragraph 1 of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Research on stored human specimens or data

From OHSR Information Sheet 15:
Research often involves the use of stored human specimens or data. Such use obliges research investigators and Institutional Review Boards (IRBs) to consider the rights and welfare of the individuals who provide them, especially when samples retain identifiers or codes. Individuals (sources) who provided specimens or from whom information was obtained in the past are no less deserving of protection than are prospective research subjects. The research use of existing specimens or data without the ability or intent to identify the source may pose little risk to the donors. However, when these sources can be identified, conflicts may arise between their rights and the scientific benefit that can be obtained from studying their stored samples.

This information sheet provides actions that must take place before IRP researchers may use stored specimens or data for research purposes. It is the policy of the NIH's Intramural Research Program (IRP) that prospective and continuing NIH IRB review and approval is required for the research use of stored human samples or data when IRP researchers or members of the research team can identify the sources.

The following definitions, policy and implementation discussion are consistent with the report of the National Bioethics Advisory Commission (NBAC) in August 1999, entitled "Research Involving Human Biological Materials: Ethical Issues and Policy Guidance." (Volume I. Report and Recommendations of the National Bioethics Advisory Commission, Rockville, Maryland, August 1999.), and the requirements of the Office of Human Research Protections (OHRP), DHHS.

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)).
2. At the NIH, the following research activities are not considered research involving human subjects: the collection and study of:
    a. Samples from deceased individuals;
    b. Samples taken for diagnostic purposes only;
    c. Specimens or data that are available from commercial or public repositories or registries;
    d. Established cell lines that are publicly available to qualified scientific investigators, and
    e. Self-sustaining, cell-free derivative preparations including viral isolates or cloned DNA.
3. Human specimens/samples include blood and other body fluids, tissues, DNA and other direct derivatives from human tissues.
4. Human data include responses to questionnaires or surveys, medical histories, records and diagnoses.
5. Source means the individual who provided the sample or from whom data were collected.
6. Identified means samples or data that are still attached to a readily available subject identifier such as a name, social security number, address, telephone number, medical record number, etc.

7. Coded means that collected samples or data are unidentified for research purposes by use of a random or arbitrary alphanumeric code but the samples may still be linked to their sources through use of a key to the code available to an investigator or collaborator.
8. Unlinked means human data or samples that were initially collected with identifiers but, before research use, have been irreversibly stripped of all identifiers by use of an arbitrary or random alphanumeric code and the key to the code is destroyed, thus making it impossible for anyone to link the samples to the sources. This does not preclude linkage with existing clinical, pathological, and demographic information before subject identifiers are removed.
9. Unidentified means that the samples or data were collected without identifiers of any kind. Samples or data may retain demographic or diagnostic information and still be considered unidentified if such information cannot be used to reveal the identity of the source.
10. Exempt research means research that is exempt from the regulatory requirement for prospective IRB review and approval. This includes "research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects" {45 CFR 46.101(b)(4)}.

POLICY:

1. The research use of stored identified or coded specimens or data, when IRP researchers can identify the sources, must receive prospective and continuing NIH IRB review and approval. This includes research protocols where the remaining research activities are limited to data analyses, and 2) the subsequent research use of specimens or data previously collected under now-terminated protocols.
2. The research use of stored coded samples when IRP researchers cannot identify subjects, such as the receipt of coded samples from non-NIH collaborators may or may not require NIH IRB review and approval. Before receiving such samples, IRP researchers must contact OHSR for guidance.
3. The research use of stored, unlinked or unidentified samples may be exempt from the need for prospective IRB review and approval. Exemption requests must be submitted in writing to OHSR. Only OHSR is authorized to determine whether a research activity is exempt.

IMPLEMENTATION: Implementing the NIH requirements for research activities with stored human specimens involves addressing the following issues:

1. Is the proposed research activity "human subjects research"? Researchers engaged in activities which are not considered research involving human subjects (see Definition 1., above) do not need IRB or OHSR review and approval; however, these activities may be subject to other requirements such as rules governing technology transfer. For any other research use of human samples, specimens or data, only an NIH IRB or OHSR may make the determination of whether the research involves human subjects. The final responsibility rests with the OHSR.
2. How does an IRP investigator obtain approval to use stored anonymized specimens? The research use of existing unidentified or unlinked samples or data is generally exempt from the requirement for prospective IRB review and approval. Exemptions are issued only by OHSR and may be sought by completing Form #1, "Request for Review of Research Activity Involving Human Subjects" available from that office or on the OHSR homepage http://ohsr.od.nih.gov/info/info.html. NIH investigators

should not make determinations about exemptions without consulting OHSR. Research involving stored identifiable or coded samples or data, when IRP investigators can identify the sources, must receive prospective and continuing NIH IRB approval.

3. What points must an NIH IRB consider in reviewing a request for the research use of stored identified or coded specimens or data when an IRP researcher can identify the source? The investigator must submit a written request (i.e., a memorandum or protocol) to the IRB which includes the following:
   a. The nature of the proposed research including a complete description of the samples or data;
   b. A justification for retention of the identities or codes of the sources of samples or data, and, in the case of codes, a description of the ease or difficulty with which linkage can be made between the code and the source, and a description of who can make the linkage.
   c. A description of the extent to which confidentiality of research data will be maintained;
   d. The informed consent document to be utilized, or a request for waiver of informed consent. When research involves stored samples or data previously collected under now-terminated protocols, an important question is whether a consent signed in the collection protocol is sufficient for the proposed research activity. The IRB will pay special attention to requests for waiver of informed consent. In order to waive informed consent, Federal regulations currently require that an IRB must find and document in its minutes that all of the following four conditions have been met:
      1) The research involves no more than minimal risk;
      2) The waiver will not adversely affect the rights and welfare of the subjects;
      3) The research could not practicably be carried out without the waiver; and
      4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   e. In those cases where a waiver of informed consent is sought, a statement that a source will not be contacted by anyone connected with the research without prior approval by the IRB.
   f. A description of how the samples, specimens and/or data will be stored; how they will be tracked; what will happen to the samples/specimens/data at the completion of the protocol; what circumstances would prompt the PI to report to the IRB loss or destruction of samples.

   The IRB will review the research in keeping with the requirements of the NIH Human Research Protection Program (HRPP) and as set forth in the NIH IRP Standard Operating Procedures.
4. What happens after an NIH IRB approves the research? Continuing IRB review and approval of the research must take place at least annually. Research protocols that require full IRB review for their initial reviews generally require it for their continuing reviews. The expedited review process may be used when:
   a. The protocol is permanently closed to enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or
   b. Where no subjects have been enrolled and no additional risks have been identified; or
   c. Where the remaining research activities are limited to data analyses.
5. What review is necessary for research collaborations involving sending or receiving stored specimens or data? For discussion of IRP guidelines on research collaborations, please review the information found in The Gray Booklet at http://ohsr.od.nih.gov/guidelines/

Prospective and continuing NIH IRB review and approval is required for research collaborations in which IRP researchers send coded samples (for which they maintain the key) to non-NIH investigator(s). The protocol must identify the names of the collaborating researchers and their affiliated institutions. Before sending the samples, IRP investigators should contact an IC technology development coordinator for guidance on an appropriate NIH transfer agreement. IRP researchers whose collaborations involve the receipt of samples collected and sent by non-NIH researchers from non-NIH subjects should contact OHSR for guidance.

If you have questions, contact your NIH IRB Chair or OHSR. OHSR is located in Building 10, Room 2C146, (p) 301-402-3444 and (fax) 301-402-3443. The web site is http://ohsr.od.nih.gov/

OHRP Guidance on human biological specimens:

SCOPE: This document applies to research involving coded private information or human biological specimens (hereafter referred to as specimens) that is conducted or supported by HHS. This document does the following:

1. Provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46).
2. Reaffirms OHRP policy (see OHRP guidance on repository activities http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm and research on human embryonic stem cells http://www.hhs.gov/ohrp/humansubjects/guidance/stemcell.pdf) that, under certain limited conditions, research involving only coded private information or specimens is not human subjects research.
3. Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.
4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

NOTE: Some HHS conducted or supported research involving coded private information or specimens may be subject to Food and Drug Administration (FDA) regulations. The FDA regulatory definitions of human subject (21 CFR 50.3(g), 21 CFR 56.102(e)) and subject (21 CFR 312.3(b), 21 CFR 812.3(p)) differ from the definition of human subject under HHS regulations at 45 CFR 46.102(f). This guidance document does not apply to research regulated by FDA that involves coded private information or specimens. Anyone needing guidance on such FDA-regulated research should contact the FDA.

TARGET AUDIENCE: Institutional review boards (IRBs), investigators, and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

BACKGROUND: HHS regulations define research at 45 CFR 46.102(d) as follows:

1. Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
2. HHS regulations define human subject at 45 CFR 46.102(f) as follows:
   a. Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains
      1) data through intervention or interaction with the individual, or
      2) identifiable private information.
3. Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for

research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

For purposes of this document, coded means that:

1. Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and
2. A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

OHRP considers the term "investigator" to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to:

1. The study, interpretation, or analysis of the data resulting from the coded information or specimens; and
2. Authorship of presentations or manuscripts related to the research.

GUIDANCE: Under the definition of human subject at 45 CFR 46.102(f), obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and
2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through

coding systems. For example, OHRP does not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

1. The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
2. The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    a. The investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
    b. There are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
    c. There are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This guidance applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects under the HHS regulations. Unless this human subjects research is determined to be exempt under HHS regulations at 45 CFR 46.101(b), IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent under HHS regulations at 45 CFR part 46.116(c) or (d).

Who Should Determine Whether Human Subjects are Involved in Research

OHRP recommends that institutions have policies in place that designate the individual or entity authorized to determine whether research involving coded private information or specimens constitutes human subjects research. The person(s) authorized to make the determination should be knowledgeable about the human subject protection regulations. In addition, the institution should ensure the appropriate communication of such a policy to all investigators. OHRP recommends that investigators not be given the authority to make an independent determination that research involving coded private information or specimens does not involve human subjects.

Research not Involving Human Subjects Versus Exempt Human Subjects Research

OHRP is aware that questions often are raised regarding the distinction between research involving private information or specimens that does not involve human subjects (as above) and human subjects research that is exempt from the requirements of HHS regulations at 45 CFR part 46. This distinction can be made easier by always using the following sequential assessment when evaluating a particular activity conducted or supported by HHS:

1. Does the activity involve research? If yes, proceed to question (2). If no, 45 CFR part 46 does not apply to the activity.
2. Does the activity involve human subjects? If yes, proceed to question (3). If no, 45 CFR part 46 does not apply to the activity. In analyzing a particular activity under the second question, it is important to focus on what is being obtained by the investigators. If the investigators are not obtaining either data through intervention or interaction with living individuals, or identifiable private information, then the research activity does not involve human subjects. Therefore, no assessment of the research activity using the third question below regarding exemptions is required because the exemptions provided for under 45 CFR 46.101(b) apply only to research involving human subjects.
3. Is the activity exempt under HHS regulations at 45 CFR 46.101(b)? If yes, 45 CFR part 46 does not apply. If no, 45 CFR part 46 does apply.

With respect to research involving private information and specimens, the exemption that is most frequently relevant is the exemption under HHS regulations at 45 CFR 46.101(b)(4):

Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

Having determined under the second question above that a research activity involves human subjects because the investigators are obtaining identifiable private information or specimens, assessment under the exemption at 45 CFR 46.101(b)(4) focuses, in part, on: (1) whether the data or specimens are existing at the time the research is proposed to an institutional official or IRB for a determination of whether the research is exempt, and (2) how the data or information is recorded by the investigators. This exemption would not apply if the investigators, having obtained identifiable private information or specimens from existing records or specimens, record the data or information in a coded manner, since the code would enable subjects to be identified through identifiers linked to the subjects.

To demonstrate how the determination of whether a research study is human subjects research differs from the determination of whether a human subjects research study is exempt under 45 CFR 46.101(b)(4), consider the following examples, in which an investigator obtains health information of living patients who were treated for arthritis with either Drug A or Drug B. The investigator obtains this information in order to evaluate and compare the treatment outcomes associated with these two drugs:

1. An investigator obtains only coded information on the treatment outcomes of patients treated for arthritis with Drug A versus Drug B from the patients' treating physician. The only involvement of

the treating physician is to provide coded information to the investigator. The investigator and the treating physician enter into an agreement prohibiting the release of the key to decipher the code to the investigator under any circumstances, until the individuals are deceased. In this example, the investigator is not conducting human subjects research because the investigator cannot readily ascertain the patients' identity.

2. An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients' existing individually identifiable medical records at the clinics where the patients were treated. The investigator records the patients' treatment outcomes in a coded manner that could permit the identification of the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. The study would not be exempt under 45 CFR 46.101(b)(4) since the investigator is recording the information in a coded manner, thus allowing the subjects to be identified indirectly through identifiers linked to the subjects.
3. An investigator obtains individually identifiable information on the treatment outcomes of patients treated for arthritis with either Drug A or Drug B by viewing patients' existing individually identifiable medical records at the clinics where the patients were treated. The investigator records only patient age, sex, diagnosis, treatment, and health status at the end of 6 months of treatment so that the investigator cannot link the recorded information back to the patients. In this example, the investigator is conducting human subjects research because the investigator is obtaining identifiable private information from patients' (and now subjects') medical records. However, the study would be exempt under 45 CFR 46.101(b)(4) since the investigator records the information in such a manner that subjects cannot be identified either directly or indirectly through identifiers linked to the subjects.

Research on fetal tissue

1. Establishment of program
    a. In general - The Secretary may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes.
    b. Source of tissue - Human fetal tissue may be used in research carried out regardless of whether the tissue is obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.
2. Informed consent of donor
    a. In general - Human fetal tissue may be used only if the woman providing the tissue makes a statement, made in writing and signed by the woman, declaring that—
        1) The woman donates the fetal tissue for use in research described in the above sections;
        2) The donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue; and
        3) The woman has not been informed of the identity of any such individuals.
    b. Additional statement - In research carried out under subsection (a), human fetal tissue may be used only if the attending physician with respect to obtaining the tissue from the woman involved makes a statement, made in writing and signed by the physician, declaring that—
        1) In the case of tissue obtained pursuant to an induced abortion—
            a) The consent of the woman for the abortion was obtained prior to requesting or obtaining consent for a donation of the tissue for use in such research;
            b) No alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue; and
            c) The abortion was performed in accordance with applicable State law;
        2) the tissue has been donated by the woman in accordance with paragraph (1); and
        3) full disclosure has been provided to the woman with regard to—
            a) Such physician's interest, if any, in the research to be conducted with the tissue; and
            b) Any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care.
3. Informed consent of researcher and donee - In research carried out under subsection (a), human fetal tissue may be used only if the individual with the principal responsibility for conducting the research involved makes a statement, made in writing and signed by the individual, declaring that the individual—
    a. Is aware that
        1) The tissue is human fetal tissue;
        2) The tissue may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth; and
        3) The tissue was donated for research purposes;
    b. has provided such information to other individuals with responsibilities regarding the research;
    c. will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and
    d. has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.
4. Availability of statements for audit-

a. In general - In research carried out under subsection (a), human fetal tissue may be used only if the head of the agency or other entity conducting the research involved certifies to the Secretary that the statements required under subsections (b)(2) and (c) will be available for audit by the Secretary.
b. Confidentiality of audit - Any audit conducted by the Secretary pursuant to paragraph (1) shall be conducted in a confidential manner to protect the privacy rights of the individuals and entities involved in such research, including such individuals and entities involved in the donation, transfer, receipt, or transplantation of human fetal tissue. With respect to any material or information obtained pursuant to such audit, the Secretary shall—
    1) Use such material or information only for the purposes of verifying compliance with the requirements of this section;
    2) Not disclose or publish such material or information, except where required by Federal law, in which case such material or information shall be coded in a manner such that the identities of such individuals and entities are protected; and
    3) Not maintain such material or information after completion of such audit, except where necessary for the purposes of such audit.

5. Applicability of state and local law-
    a. Research conducted by recipients of assistance - The Secretary may not provide support for research unless the applicant for the financial assistance involved agrees to conduct the research in accordance with applicable State law.
    b. Research conducted by Secretary - The Secretary may conduct research under this section only in accordance with applicable State and local law.
6. Report- The Secretary shall annually submit to the Committee on Energy and Commerce of the House of Representatives, and to the Committee on Labor and Human Resources of the Senate, a report describing the activities carried out under this section during the preceding fiscal year, including a description of whether and to what extent research under this section has been conducted in accordance with this section.
7. Definition- For purposes of this section, the term `human fetal tissue' means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth.'.

Purchase of human fetal tissue; solicitation of acceptance of tissue as directed donation for use in transplantation.

Part G of title IV of the Public Health Service Act, as amended by section 111 of this Act, is amended by inserting after section 498A the following section:

Prohibitions Regarding Human Fetal Tissue - SEC. 498B.

1. Purchase of tissue- It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration if the transfer affects interstate commerce.
2. Solicitation or acceptance of tissue as directed donation for use in transplantation - It shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purpose of transplantation of such tissue into another person if the donation affects interstate commerce, the tissue will be or is obtained pursuant to an induced abortion, and—

a. The donation will be or is made pursuant to a promise to the donating individual that the donated tissue will be transplanted into a recipient specified by such individual;
b. The donated tissue will be transplanted into a relative of the donating individual; or
c. The person who solicits or knowingly acquires, receives, or accepts the donation has provided valuable consideration for the costs associated with such abortion.

3. Criminal penalties for violations-
   a. In general - Any person who violates this subsection shall be fined in accordance with title 18, United States Code, or imprisoned for not more than 10 years, or both.
   b. Penalties applicable to persons receiving consideration - With respect to the imposition of a fine, if the person involved violates this section, a fine shall be imposed in an amount not less than twice the amount of the valuable consideration received.
4. Definitions - For purposes of this section:
   a. The term `human fetal tissue' has the meaning given such term in section 498A(f).
   b. The term `interstate commerce' has the meaning given such term in section 201(b) of the Federal Food, Drug, and Cosmetic Act.
   c. The term `valuable consideration' does not include reasonable payments associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue.'.
   d. Nullification of Moratorium. In general - No official of the executive branch may impose a policy that the Department of Health and Human Services is prohibited from conducting or supporting any research on the transplantation of human fetal tissue for therapeutic purposes. Such research shall be carried out in accordance with section 498A of the Public Health Service Act (as added by section 111 of this Act), without regard to any such policy that may have been in effect prior to the date of the enactment of this Act.

Prohibition Against Withholding of Funds in Cases of Technical and Scientific Merit -

1. In general - Subject to subsection (b)(2) of section 492A of the Public Health Service Act (as added by section 101 of this Act), in the case of any proposal for research on the transplantation of human fetal tissue for therapeutic purposes, the Secretary of Health and Human Services may not withhold funds for the research if—
   a. the research has been approved for purposes of subsection (a) of such section 492A;
   b. The research will be carried out in accordance with section 498A of such Act (as added by section 111 of this Act); and
   c. There are reasonable assurances that the research will not utilize any human fetal tissue that has been obtained in violation of section 498B(a) of such Act (as added by section 112 of this Act).
2. Standing approval regarding ethical status- In the case of any proposal for research on the transplantation of human fetal tissue for therapeutic purposes, the issuance in December 1988 of the Report of the Human Fetal Tissue Transplantation Research Panel shall be deemed to be a report--(A) issued by an ethics advisory board pursuant to section 492A(b)(5)(B)(ii) of the Public Health Service Act (as added by section 101 of this Act); and (B) finding, on a basis that is neither arbitrary nor capricious, that the nature of the research is such that it is not unethical to conduct or support the research.

Authority for withholding funds from research

In the case of any research on the transplantation of human fetal tissue for therapeutic purposes, the Secretary of Health and Human Services may withhold funds for the research if any of the conditions specified in any of subparagraphs (A) through (C) of subsection (b)(1) are not met with respect to the research.

Definition

For purposes of this section, the term `human fetal tissue' has the meaning given such term in section 498A(f) of the Public Health Service Act (as added by section 111 of this Act).

Blinded, randomized controlled trials

From OHSR Information Sheet 13:
In March, 1998, a subcommittee of the NIH Human Subjects Research Advisory Committee (HSRAC) was constituted to examine what information is usually disclosed to research subjects enrolled in Clinical Center studies where the research design prevents them knowing at the outset the experimental treatment or drug they will receive. Such studies are normally called randomized, controlled or placebo trials and the subjects, and often the investigators as well, are "blinded" to certain information in order to reduce bias.

The HSRAC subcommittee was given three tasks (see headings below), and after evaluation, provided the following report and offered recommendations which the full HSRAC endorsed in July, 1998. The subcommittee recommendations are provided as guidance for investigators and IRBs.

1. Review Clinical Center consent documents used in randomized, blinded studies to evaluate language generally used about unblinding. The subcommittee reviewed 41 consent documents from active Clinical Center protocols that included blinded design. Some did not discuss blinding in the consent at all. Some described blinding in language such as "neither you nor your doctor (health care providers) will know which treatment you are on." A few indicated that another person, such as a pharmacist in the NIH pharmacy would have this information. In a few consent documents, a rationale was given for blinding "so that the effectiveness of the drug can be accurately evaluated" or "to maintain an equal expectation of benefit between two groups." In a few cases, it was added that this practice (of blinding) "respects the sacrifices made by all of the patients who participated in early stages of the trial. If the results are compromised by premature disclosure of results, their sacrifice, whether of risk, pain, or difficulty, might have been in vain." Fewer consent documents mentioned when or in what conditions information about treatment assignment would be provided to participants at the completion of the study. In a few documents, statements about the timing of sharing information suggest to subjects that they might receive information at the completion of their involvement (rather than at the completion of the study), e.g. "After you have completed the study, we will share this information with you"; or "This information may be divulged to you after testing is complete." Only a few consent documents made any reference to the possibility of breaking the blind in the event of a medical emergency.

   Subcommittee Recommendations: In studies that employ a randomized blinded approach, both randomization and blinding should be explained in simple terms in the consent document. The explanation should include the meaning of randomization, placebo (if used), and blinding; why these methods are being used; who has the ability to identify treatment assignments (who has the code); when and in what conditions the blind may be broken; and when information about treatment assignment will be shared with the subject. It should be made clear whether information is to be shared at the completion of the study rather than when the subject personally completes the study.

2. Determine if it is appropriate ever, and in what circumstances, to permit unblinding before the end of the study. Random assignment and blinding are methods used in clinical trials to reduce bias and enhance study validity. Both require justification, however, because when randomized and blinded,

subjects have no say in their choice of experimental treatment nor do they have information about what experimental treatment they are receiving. In addition, many studies have documented that in blinded trails, subjects and investigators often can guess (more frequently than by chance) whether they are on active drug or placebo. In the scientific design and review of a given protocol, the necessity and adequacy of blinding and randomization should always be assessed. Once blinding is chosen as an appropriate method for a particular protocol, there are two main ethical concerns:

a. Information about which intervention the subject is receiving may be relevant to his/her autonomous decisions; and
b. Information about which intervention the subject is receiving may be important in managing an adverse event or a medical emergency.

With respect to the first concern, if subjects consent to the study and its purpose, they may also consent to suspend knowledge about which intervention they are receiving until study completion or some other predetermined timepoint. To consent, they should understand explicit information provided to them about blinding (as described in #1 above) and agree to the suspension of knowledge. The subject who does not agree to suspend knowledge until study completion should not be included in the study.

With respect to the concern about subject safety, knowledge of which medications the subject is receiving may be relevant to treating adverse events or other medical emergencies. Therefore, investigators should consider these issues in advance and explicitly outline in the protocol the conditions in which adverse events would trigger the breaking of the blind. In some cases, for example, knowing the medication would not alter the management of an emergent or adverse event, whereas in other cases, such knowledge would make a difference.

Subcommittee Recommendations. To balance the need for scientific objectivity with respect to a research subject's need for information to make autonomous decisions, investigators should give subjects adequate information about randomization and blinding (as described in recommendation #1) and ask subjects to consent to a suspension of knowledge about their experimental treatment assignment until the completion of the protocol.

To balance the need for scientific objectivity with the concern for subject safety, investigators should consider in advance the conditions in which a blind may be broken to treat an adverse event. Specifically, they should include a description in the protocol of where the code is located, the circumstances (if any) in which the code will be broken, who will break it, how the information will be handled (i.e. will the investigator, the subject, the IRB, and the treating physician be informed?), and how breaking of a blind will influence analysis of the data. The subject should also have information about whom to notify in the event of an emergency. The IRB should be satisfied that the plan provides for adequate protection of subject privacy.

3. Consider in what circumstances it is appropriate for an IRB to receive information about which subjects are on active drug or placebo. The IRB is responsible for knowing that subject welfare is protected and that "the research plan has adequate provisions for monitoring data collected to ensure the safety of subjects" [45 CFR 46.111(6)]. The IRB also has a responsibility to assure that the

proposed research methodology will provide useful and valid information. In this light, all protocols which involve an experimental intervention, including those that involve randomization and blinding, should have a predetermined rating system for evaluating adverse events (this could be a graded toxicity scale such as that used by the NCI or a simple dichotomous definition of serious vs. non-serious adverse events as dictated by the FDA). The IRB should satisfy itself at the initial review of a protocol that procedures for identifying and reporting adverse events are planned and adequate. In some cases, even for single site Clinical Center studies, a Data and Safety Monitoring Board (DSMB) may be an appropriate mechanism for assuring regular review of research data. In trials that do not have a DSMB, the details of what incidence or severity of foreseeable adverse events would trigger modifications in the trial or in the management of an individual subject (including in what circumstances the blind would be broken) should be spelled out, as well as a mechanism for dealing with unpredictable events. These issues are important to the IRB both for the safety of the individual subject as well as to allow evaluation of risks and informed consent for all other (and future) subjects of the study. After the occurrence of an adverse event, while considering appropriate management of the subject, as well as the risk-benefit analysis and informed consent of other subjects, the IRB may determine in some cases that breaking the blind is unnecessary. In other cases, the IRB may decide that the information about experimental assignment is vital to their deliberations.

Subcommittee Recommendation. For protocols that involve an experimental intervention, including but not limited to those which employ randomization and blinding, the IRB should be satisfied that the plan for monitoring subjects and identification and reporting adverse events is appropriate and adequate. The IRB should be informed of the method that will be used to rate adverse events, the plan for managing adverse events, and how the protocol might be modified for predictable or unpredictable adverse events. When an adverse event is reported to it, the IRB should decide whether or not maintaining the blind jeopardizes the welfare of the individual subject and/or other subjects on the same study.

HIV Testing in research

From OHRP Guidance:
Informing of test results/counseling

It is the policy of the Public Health Service (PHS) that when HIV testing is conducted or supported by PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided with the opportunity to receive appropriate counseling. This policy applies to all intramural and to all extramural PHS activities, including both research and service activities, domestic and foreign. Individuals may not be given the option "not to know" the result, either at the time of consenting to be tested or thereafter. This policy does not apply to testing situations in which subjects consent to be tested but specimen results cannot be linked to individual subjects by anyone other than the subjects themselves. The PHS encourages testing facilities to advise test subjects to obtain test results and to abstain from risk behaviors.

Exceptions

1. Pertaining to an Individual. Where there are compelling and immediate reasons that justify not informing a particular individual that he or she is seropositive, e.g., indicating that an individual would attempt suicide, the particular individual need not be informed of HIV test results. When this exception is made to the policy of informing individuals, the details of the exception shall be documented by the responsible individuals at the testing facility. If this exception is involved in the context of a research study, the principal investigator shall promptly report the exception to the local Institutional Review Board (IRB) without identifying the individual.
2. Pertaining to Protocol Design. Because circumstances may exist in which extremely valuable knowledge might be gained from research involving subjects who would be expected to refuse to learn their HIV antibody results, an exception included in the protocol design may be proposed to the IRB reviewing the research proposal. The IRB shall consider the particular circumstances of the research study, the characteristics of the target research subjects, and other factors, and may approve a testing procedure that would allow research subjects to participate without being informed of their individual results. In proposing such an exception, the investigator must demonstrate to the satisfaction of the IRB that:
    a. Research subjects will be informed of their risk of infection;
    b. Research subjects will receive risk reduction counseling whether or not they receive their test results;
    c. There is good reason to believe that a requirement for test result notification would significantly impair collection of study information that could not be obtained by other means; and
    d. The risk/benefit ratio to individuals, their partners, and society will be periodically reevaluated by the IRB so that the study might be revised or terminated if it is determined that it is no longer justifiable to allow subjects to continue to participate without receiving their HIV test results.
3. Pertaining to Foreign Sites. Activities conducted at foreign sites should be carefully evaluated to account for cultural norms, the health resource capabilities and official health policies of the host country. If a research protocol review is involved, the reviewing IRB must consider if any

modification to the policy is significantly justified by the risk/benefit evaluation of the research. The IRB might wish to seek expert advice, e.g., local public health experts, in evaluation of these projects.

Review of Exceptions

The Agency Head (or designee) must specifically approve any proposed exception described under 2 or 3 above that is to be funded or conducted by the PHS agency whether a research activity or a service activity and whether domestic or foreign.

For research activities under 2 or 3, IRB approval must be obtained before the approval of the Agency Head is sought. In addition, the Office for protection from Research Risks (OPRR), NIH, is to be notified of the requested exception prior to or simultaneous with request for approval for an exception from the Agency Head.

Assessment of Current Activities

Any ongoing PHS activity that currently provides for an option "not to know" shall implement this policy for all persons tested hereafter. Individuals tested prior to the issuance of this policy, whose inform consent was given under the condition that they may choose not to learn their test results, may continue to decline to be informed. Every reasonable effort should be made to encourage such individuals to learn their results, however, and the individuals should be counseled about risk behaviors. The appropriate Agency Head, and OPRR if a research activity is involved, shall be informed of such ongoing activities.

In ongoing HIV-related research studies, no additional research subjects may be entered as participants without being required to be informed of their results unless exceptions are approved by the IRB and Agency Head, as described above.

Counseling

Any person tested for HIV infection should receive the results of his or her tests and counseling in a timely fashion from an individual qualified to provide test counseling and partner notification services.

PHS POLICY ON PARTNER NOTIFICATION

Introduction

1. This policy provides PHS health care personnel with guidance regarding their obligation to notify sex and needle-sharing partners* of HIV-infected individuals who are cared for by these personnel as part of their official duties at a PHS facility. The policy is intended to cover only the limited circumstances where the personnel are employed by the PHS at a PHS facility.
    a. Refers to current and recent sex and needle-sharing partners (i.e., at least those within the last 12 months) and hereafter will be referred to in this policy only as "partners."

b. The policy does not cover contractors, grantees, or PHS personnel on detail to non-PHS facilities. However, PHS Agency Heads have discretion and are encouraged, where appropriate, to extend the policy to contractors carrying out activities at PHS facilities.
c. PHS Agency Heads may also issue instructions and guidelines in implementation of this policy, as long as the instructions and guidelines are consistent with the policy.

2. The policy addresses instances where, in the course of carrying out PHS activities, including post-test counseling, PHS personnel learn the name of an HIV-infected individual and the names of partners. The policy in no way affects anonymous testing or requires PHS personnel to collect the names of HIV- infected individuals and their partners if personnel would not otherwise do so in carrying out their PHS responsibilities.

Partner notification

To the extent possible, known partners of a person with HIV infection shall be notified that they may have been exposed to HIV and should be encouraged to be counseled and tested. Under usual circumstances, this process is preferably carried out in collaboration with HIV prevention activities of local public health departments.

Applicability

This policy is applicable to clinical activities at PHS facilities carried out by PHS personnel, where there is a physician-patient relationship or health care is otherwise provided. The facilities involved are (1) the NIH Clinical Center, (2) Indian Health Service hospitals and clinics, (3) employee health clinics, and (4) other PHS facilities engaged in clinical activities of a similar nature.

Informed Consent

When identifiers are to be collected (i.e., information which can link test results to an identifiable individual), testing for HIV infection is to be carried out only with the informed consent of the individual to be tested. As part of the consent, the individual shall be informed that in the event of a confirmed HIV positive test (1) the individual will be so advised and expected to inform all partners, and (2) if the individual is unwilling or unable to notify such partners, the PHS facility will take steps to do so or otherwise satisfy itself that notification will be made.

Counseling

To ensure that accurate and useful information regarding the implications of infection with HIV are available, whenever practical, PHS facilities should have trained counselors available to advise HIV-infected individuals and their partners. In the absence of trained counselors, or where geographically not feasible, PHS facilities shall develop arrangements for such counseling by other trained counselors, for example, those from local health departments. Such counseling preferably should be provided on-site at the time of the initial notification. Post-test counseling should be provided to all persons tested, whether seropositive or not.

Whether, or not PHS personnel have the names of infected individuals or specific partners, counseling of a person with HIV infection shall include emphasis on the importance of notifying partners and urging them to be counseled and tested.

Notification

Notification of partners remains the primary responsibility of each individual who tests positive. Effort shall be made to persuade the individual (1) to carry out this responsibility and (2) to indicate to partners that counseling and testing are available or can be arranged through the PHS facility.

Each PHS facility shall develop procedures (e.g., in collaboration with HIV prevention activities of local health departments) for (1) verifying that current and recent partners have been notified, where the HIV-infected individual has agreed to do the notifying, and (2) notifying or assuring the notification of partners, whenever possible, where their identities are known to the facility but the HIV-infected individual is not willing or able to notify them.

Confidentiality

When the PHS facility undertakes a process of partner notification, confidentiality shall be maintained by not releasing or acknowledging the identity of the HIV-infected individual to partners or the identity or medical status of any partners who may be seen as a result of notification activities.

Exceptions

1. PHS Agency Heads may grant exceptions to this policy on a case by case basis in which compelling, documented circumstances militate against notification. This authority may be delegated to personnel not lower than that of branch chief or equivalent.
2. PHS Agency Heads may grant exceptions to this policy for a class or group of patient, with the prior approval of the Assistant Secretary for Health, in special circumstances where compelling, documented, public health considerations justify a class or group exception.
3. Where an individual has previously been found to have HIV infection and has undergone counseling and partner notification activities, there may be no necessity to have the process repeated. This determination in each case should be made by the PHS facility based upon whether information concerning additional partners has come to the facility's attention.

Certificates of Confidentiality

From OHRP Guidance:
Scope: The purpose of this document is to provide guidance about Certificates of Confidentiality and assistance in locating resources for obtaining a Certificate of Confidentiality to protect the privacy of research subjects.
Target Audience: Institutions, institutional review boards (IRBs), and investigators.
Background: The Public Health Service Act 301(d), 42 U.S.C. 241(d), "Protection of privacy of individuals who are research subjects," states:

The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.

The privacy of the research subjects referred to in 301(d) is protected through the issuance of Certificates of Confidentiality. These certificates of Confidentiality provide protection against compelled disclosure of identifying information about subjects enrolled in sensitive biomedical, behavioral, clinical, or other research. This protection is not limited to federally supported research.

Guidance: OHRP does not issue Certificates of Confidentiality. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) and other HHS agencies to protect identifiable research information from forced or compelled disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects, such as damage to their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help to minimize risks to subjects by adding an additional level of protection for maintaining confidentiality of private information.

Certificates of Confidentiality protect subjects from compelled disclosure of identifying information but do not prevent the voluntary disclosure of identifying characteristics of research subjects. Researchers, therefore, are not prevented from voluntarily disclosing certain information about research subjects, such as evidence of child abuse or a subject's threatened violence to self or others.

However, if a researcher intends to make such voluntary disclosures, the consent form should clearly indicate this. Furthermore, Certificates of Confidentiality do not prevent other types of intentional or unintentional breaches of confidentiality. As a result, investigators and IRBs must ensure that other appropriate mechanisms and procedures are in place to protect the confidentiality of the identifiable private information to be obtained in the proposed research.

For more information on Certificates of Confidentiality and their limitations, see
http://grants.nih.gov/grants/policy/coc/index.htm
For Certificate of Confidentiality contacts at the National Institutes of Health, see
http://grants.nih.gov/grants/policy/coc/contacts.htm

For information on obtaining a Certificate of Confidentiality for research supported by other HHS agencies, please contact the appropriate program official. Again, please note that the OHRP does not issue Certificates of Confidentiality.

HIPAA Privacy Rule and NIH intramural research

The privacy rule of the Health Insurance Portability and Accountability Act (HIPAA) applies to covered entities, such as health care providers, health plans, and health care clearinghouses. The HIPAA Privacy Rule for the first time creates national standards to protect individuals' medical records and other personal health information. HIPAA gives patients more control over their health information, sets boundaries on the use and release of health records, establishes appropriate safeguards for health care providers and others to protect the privacy of health information, limits release of information to the minimum reasonably needed for the purpose of the disclosure, gives patients the right to examine and obtain a copy of their own health records and request corrections, and empowers individuals to control certain uses and disclosures of their health information. Violators of HIPAA can face civil and criminal penalties. Though HIPAA provides strong protection for privacy rights, it supports some involuntary disclosures to protect third parties or society. The NIH is not a covered entity under HIPAA. Even so, it is important for NIH researchers to be aware of HIPAA because they may be collaborating with researchers who will be affected by HIPAA, such as researchers at hospitals or medical centers.

NIH HIPAA link: http://www.hhs.gov/ocr/hipaa/
Privacy and research: http://privacyruleandresearch.nih.gov/

Appendix A – Forms

Below is a list of documents that are available from the NIEHS/NIH websites. More documents will become available in the future.

Exempt research
Request for an exemption from OHSR: http://ohsr.od.nih.gov/info/pdf/requestforReview.doc

New Protocols
1. NIH-1195 form, PDF version: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/1195.pdf
2. WORD version: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/niehs_irb_standard_format_04.doc
3. Protocol in Standard Format: [Under development]
4. Targeted/planned enrollment table: http://ohsr.od.nih.gov/irb/Attachments/6-6_Target_Population_Repor.doc
5. Initial review checklist: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/ir-checklist042808.pdf
6. Clearance of Financial Holdings (Conflict of interest) form: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/pfc-form.pdf
7. NIH-2686 form: Designation of reimbursement for travel and subsistence for NIH clinical intramural research protocol: http://intranet.cc.nih.gov/ops/pdf/DTRS.pdf

Continuing Review:
1. Continuing review form: http://www.nihtraining.com/ohsrsite/irb/Attachments/6-5_1195-1_0906_Fillable.pdf
2. Continuing review checklist: http://www.niehs.nih.gov/about/orgstructure/boards/irb/docs/cr-checklist042808.pdf
3. Inclusion/enrollment report: http://ohsr.od.nih.gov/irb/Attachments/6-6_Summary_Minority_Inclus.doc