

North Texas Regional Institutional Review Board

UNT Health Science Center - Office of Research Compliance

IRB Manual Standard Operating Principles and Procedures

Revised May 1, 2018

NOTE: The Principles and Procedures outlined in this manual are for the North Texas Regional Institutional Review Board (IRB). All institutions affiliated or associated with the North Texas Regional IRB must follow these Principles and Procedures. The UNTHSC Office of Research Compliance / ORC (formerly known as the *Office for the Protection of Human Subjects or OPHS*) supports the North Texas Regional IRB. Where appropriate, references to the Office for the Protection of Human Subjects should be replaced with the North Texas Regional IRB.

Modifications to the IRB Manual

Date	Chapter/ Section	Description of Modification(s):
2/01/10	9.10 & 9.12	1) Section 9.10 modified to include additional information about re-consenting requirements when minors become adults during a research study; 2) Addition of Section 9.12 titled “Re-Consenting Subjects” to describe when investigators should once again seek informed consent from research subjects.
2/4/10	8.2	1) Requirements for CITI Refresher course changed from every 2 years to every 3 years; 2) Regulation of Human Subject Research course number updated (to BMSC 5203), and the length of time this course will satisfy the educational training requirements was changed from 5 to 6 years.
4/19/10	7.4	Clarification on Off-Site SAE reporting requirements.
5/25/10	8.11& 15.5	Added a section to Chapter 8 and Chapter 15 regarding the registration of clinical trials (ClinicalTrials.gov)
8/10/10	5.12 & 6.8	Clarification on Exempt category reporting (Section 5.12) and use of commercial IRBs (Section 6.8)
10/19/10	8.5 & 7.1	1) Clarification on reporting requirements for changes in conflict of interest disclosure status; 2) Clarification on OPHS staff approval of minor/non-substantive changes to Exempt category research
11/02/10	17.4	Clarification on suspension or termination of all research activities within a department due to one or more non-compliant investigators.
1/11/11	7.5 & 8.2	1) Addition of Section 7.5 describing protocol exceptions for investigator-initiated [non-clinical trial] studies; 2) Clarification on NIH training in the Protection of Human Subjects
1/26/11	7.4	Clarification on summary reports of SUSARs and SAEs
1/31/11	8.2	Clarification that the Good Clinical Practices (GCP) Course and the Responsible Conduct of Research (RCR) Courses are not substitutes for the Basic CITI Course in the Protection of Human Subjects
2/14/11	8.2	Clarification on Waiver of CITI Training Requirement for non-UNTHSC personnel
2/23/11	8.1	Clarification/more specific definition of who can serve as Principal Investigator (PI) at the UNT Health Science Center
4/12/11	20	Revisions to Audit Principles and Procedures
4/15/11	17.3-17.4	Section updated to include procedures for Administrative Holds/Administrative Warnings and clarification on the reporting requirements for IRB Suspension and Terminations. In addition, Section 17.3 and 17.4 were consolidated into one section. Chapter 17 title also updated.
6/10/11	8.2	The addition of an important note about human subject research education compliance and documentation.
7/19/11	9.9	Changes to the procedures for Spanish translation verification by OPHS.

9/9/11	6.8	Commercial IRB update regarding including a list of key personnel for projects utilizing a commercial IRB.
10/6/11	17.3	Administrative Hold procedures for Continuing Reviews
5/10/12	17 and 20	Modification of Chapters 17 and 20; updated Non-Compliance units as well as technical aspects of audit and re-worded procedures
7/10/2012	20	Chapter updated to include Exempt category studies; added new section (20.3) to clarify all human subject research protocols including exempt protocols can be audited; updated section numbers: 20.3 changed to 20.4, 20.4 changed to 20.5, and 20.5 changed to 20.6
7/10/2012	20.6	Changed 20.4 to 20.5
7/10/2012	TOC	Updated
10/8/2012	4.9	Sub-title revised to include “for IRB” Section modified to include how long IRB must maintain records
10/8/2012	7.6	Modified section to include Investigator recordkeeping requirements
10/8/2012	9.6	Clarification that no additional data can be written on informed consent form
10/8/2012	14.3	Revised to include all records including portable data storage devices must be maintained by Principal Investigator
2/15/2013	9.11	Modified section to include guidance and procedures for persons who are unable to read or speak (blind, illiterate, visually or verbally incapacitated)
3/21/2014	17.3	Revised section to include an additional basis for an Administrative Hold. An Administrative Hold may be placed on a protocol as a result of a post-approval monitoring audit.
03/28/14	17.3	Revised section to include a step related to an Administrative Hold as a result of post monitoring approval. More specifically, the principal investigator may voluntarily place the protocol on hold in order to amend the protocol and/or related materials to address audit findings.
08/12/14	12.3	Updated this section to adopt the OHRP definition of “prisoners” (instead of having a broader definition that included probationers). The revised definition received approval by the convened IRB on May 7, 2013, with an immediate effective date (manual updated on 08/12/14).
04/18/17	13.8 – 13.10	Updated to include IBC (Biosafety) requirements associated with human biospecimens collection; order of sub-headings also modified as a result.
07/10/17	5.4 13.8	Revised to clarify that Clinical Research Management (CRM) projects conducted at non-UNTHSC sites may be undergo a “facilitated review” by UNTHSC IRB. Updated to provide researchers with additional guidance regarding IBC (Biosafety) requirements for an IRB protocol involving human biospecimens: (1) IBC approval comes first; and (2) A single approved IBC protocol can be used for more than one IRB protocol. Minor formatting revisions made as a result of the above changes.
05/01/18	20	Revised chapter to include procedure for researchers failing to respond to Notice of Audit and failing to provide a written corrective action plan

	Cover page	<p>following a post-approval monitoring review. Minor revisions to update procedures and reduce repetition. Also, minor edits to update titles and names.</p> <p>Updated the front page to indicate the recent name change of this IRB to the “North Texas Regional Institutional Review Board.” In addition, a clarifying note that the UNTHSC Office of Research Compliance, which supports to the North Texas Regional Institutional Review Board, was formerly known as the Office for the Protection of Human Subjects (OPHS) and references to this office should be replaced with the North Texas Regional IRB.</p>
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PREFACE

Commitment of UNTHSC to Human Subjects Protection

A vast and successful research enterprise is a catalyst for societal benefits and economic well being. Thus, maintaining public trust in the nation's academic research centers is a critical national goal. An excellent Human Research Protection Program (HRPP) is a vital part of retaining this trust and assuring that priority is given to the rights and welfare of those who participate in research. At UNTHSC, protection of research subjects is a university-wide function that merits and receives the highest level of institutional support, commitment, visibility, and rigor.

Federalwide Assurance (FWA)

The Vice President for Research Administration (hereafter known as the VP for Research) at UNTHSC is the Institutional Official signatory for the purposes of Human Subjects Research protections. The UNTHSC Institutional Review Board (IRB) and the Office for the Protection of Human Subjects (OPHS) has been delegated the responsibility, by the President and the Senior Vice President for Research, to create and implement principles and procedures for Human Subjects Research to ensure compliance with federal, state, and local laws and regulations by all UNTHSC Human Subjects Researchers. This delegation has been documented with Federalwide Assurance (FWA) (Appendix A) filed with the Department of Health and Human Services. The FWA constitutes University policy and commitment, where the OPHS-IRB Manual serves to delineate and implement Federal policies and best practices.

Office for the Protection of Human Subjects (OPHS)

This office was created to manage the system for protecting human subjects in research, and oversee all aspects of the human research protection program at UNTHSC. The OPHS also supports and assists the IRB in carrying out the ethical and regulatory obligations of the IRB.

All UNTHSC research using: human subjects; human biological specimens; data gathered from human subjects in interactions or interventions; device testing on human subjects; individual private information; or studies designed to gain generalizable knowledge about classes or categories of human subjects must first be reviewed by the OPHS before any research can be initiated.

Questions about submission, review of projects, or ethical or regulatory questions regarding Human Subjects Research should be directed to the OPHS. The OPHS offers regular human subjects research education sessions for faculty, staff, and students, or at any faculty meeting or venue of their choice. Student researchers are also offered education and guidance by OPHS. Legal questions pertaining to Human Subjects regulations or UNTHSC-wide relevant policies should be addressed to the Office of University Counsel.

Once OPHS has conducted a review, the research project may be approved as is (in the case of Exempt Category projects) or referred for further review and approval by the UNTHSC Institutional Review Board (IRB). This review may take the form of an Expedited Review by the IRB Chair, Vice Chair or IRB member

as designated by the IRB Chair or Vice Chair; or the protocol may be referred by the IRB Chair or Vice Chair to be reviewed at a convened meeting of the IRB (full Board review).

Chapter 1: UNTHSC Human Research Protection Program

CHAPTER CONTENTS

- UNTHSC Human Research Protection Program (HRPP)
 - Human Subjects Protection Team
 - Office for the Protection of Human Subjects (OPHS) Organizational Chart
 - How the HRPP works together to protect subjects.
-

1.1 UNTHSC Human Research Protection Program

The University of North Texas Health Science Center (UNTHSC) operates a University-wide Human Research Protection Program (HRPP) to review and approve all research involving human subjects.

The HRPP encompasses many levels of administration and academic programs. The HRPP team consists of: the VP for Research as the Institutional Official (IO), the Director and staff of the Office for the Protection of Human Subjects (OPHS), and the Institutional Review Board (IRB) for the UNTHSC, and the IRB Chair.

Reporting to the VP for Research, the Office for the Protection of Human Subjects oversees human subjects' protections through program oversight, education, principles/procedures setting, and outreach. The IRB at UNTHSC is empowered to review all human subjects research proposals - funded or not - which are conducted by UNTHSC faculty, staff, or students, as well as designated community research partners.

The University of North Texas Health Science Center is committed to conducting its biomedical and behavioral research involving human subjects under rigorous ethical principles. The IRB has been established to comply with existing regulations of the federal government in accordance with U.S. Department of Health and Human Services (DHHS) regulations in 46 CFR 46, with the Food and Drug Administration (FDA) regulations set forth in 21 CFR 50, 56, and with Federalwide Assurance (accepted by the DHHS, Office for Human Research Protections [OHRP]).

Further, the University has agreed to adhere to the statement of ethical principles as described in *The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research* found in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; and the

IRB is cognizant of the *International Conference on Harmonization Good Clinical Practice Consolidated Guidelines* regarding organization and operation of Institutional Review Boards (IRBs).

This fundamental commitment to the protection of human subjects applies to all UNTHSC research involving human subjects regardless of whether the research is funded through government, non-profit or industry sponsors, through University funds, or not funded at all, and regardless of the location of the research.

Before *any* human subject research project is initiated, it must be reviewed and approved by the OPHS and where appropriate, the IRB. While the principal investigator has primary responsibility for the conduct of the study, the UNTHSC OPHS and IRB is responsible for protecting the rights and welfare of study subjects under FWAs granted by DHHS (http://www.hhs.gov/ohrp/assurances/assurances_index.html) to the University. The University and its researchers adhere to federal, Texas, and local regulations and laws as appropriate. Ethical and procedural guidelines by recognized organizations are also used for achieving best practices.

1.2 Human Subjects Protection Program Team

Institutional Official / Human Subjects Research

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Itzel Peña Pérez, MS, CIP	Human Subject Protection Coordinator	Itzel.Pena@unthsc.edu
Mary Wilson	Administrative Services Officer	Mary.Wilson@unthsc.edu

The OPHS conducts initial review for all research projects involving human subjects and refers their findings and recommendation to the UNTHSC IRB for formal in-depth review and approval. Further, on behalf of the IRB, OPHS is authorized to monitor all research involving human subjects under their Federalwide Assurance (FWA) jurisdiction. OPHS provides administrative support to the IRB committees, provides assistance to investigators who are preparing IRB applications, and maintains records of IRB reviews and approvals for investigators.

Institutional Review Board (IRB)

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Chair UNTHSC – IRB
Center for Bio Health (CBH-160)
3500 Camp Bowie Blvd
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Organization Chart
Office for the Protection of Human Subjects
November 2011

Thomas Yorio, PhD

Provost and Executive Vice President for Academic Affairs

David Cistola, MD, PhD

Vice President for Research

FWA Signatory (Institutional) Official

Brian A. Gladue, PhD, CIP

Director, Office for the Protection of Human Subjects

OPHS STAFF

Mary Wilson:	Provides administrative support for all OPHS and IRB related activities, including budgets, purchasing and office management; assists with IRB course curriculum
Deborah Ceron:	Specializes in Clinical Trial (drug and device) protocol reviews, amendments, modifications and Serious Adverse Events; assists in training and supervision of OPHS Interns; coordinates OPHS activities with Office of Clinical Trials
Rhonda Dash, MPH:	Conducts post-approval audits and compliance monitoring of all category research protocols involving human subjects including FDA and non-FDA regulated studies; assists with policy and procedure development and on-line outreach/education training programs directed to faculty, staff and students campus-wide
Amanda Oglesby, MS:	Reviews protocols, amendments and modifications for SPH, GSBS, and SHP; assists with policy and procedure development and outreach/education training programs directed to faculty, staff and students in SPH, GSBS, SHP and Health Institutes of Texas
Itzel Peña Pérez, MS:	Reviews protocols, amendments and modifications for SPH, TCOM and Health Institutes of Texas; also maintains and enhances OPHS-IRB web site; reviews documents for appropriate Spanish translations

1.3 How the HRPP Works to Protect Subjects

Office for the Protection of Human Subjects (OPHS)

The OPHS staff work directly with faculty, staff, and students to assist in the preparation of IRB applications, discuss any comments or complaints that the individuals may have, and answer any of their questions. In conjunction with the IRB Chair, the Director and the OPHS staff work with the UNTHSC faculty, staff and students, on all administrative, regulatory and ethical issues pertaining to research involving human subjects.

OPHS is responsible for promoting excellence in human subjects research programs across the University, overseeing the IRB, providing human subjects education, and advising the President, Provost and Executive Vice President for Academic Affairs, and VP for Research on human research issues.

The accountability within the Human Research Protection Program (HRPP) at UNTHSC begins with the OPHS staff who report to the OPHS Director. The IRB Chair works with the Director of OPHS. The Director of OPHS also reports to the VP for Research who is accountable to the Provost and Executive Vice President for Academic Affairs, who reports directly to the President of the University.

The IRB members contact the IRB Chair, the Director and OPHS staff with any questions, concerns, or suggestions that they may have. Any regulatory or IRB principles/procedures changes are provided to the members via email, direct meetings with OPHS staff, and at IRB meetings. Education sessions are held for members at the meetings and special education sessions are given on an as-needed basis.

The OPHS has regular staff meetings to ensure that any issues within the IRB can be addressed and that all staff are made aware of any new regulations or guidance that may be available. Staff problems or concerns can also be addressed at this time, or can be done on an individual basis. Issues that can benefit or educate others in the HRPP are forwarded by OPHS for discussion and distribution to the entire university community.

Chapter 2: Human Research Protection: Ethical Basis and History

CHAPTER CONTENTS

- Nuremburg Code
- Declaration of Helsinki
- NIH Policies
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- FDA 21 Part 50 and 56
- Belmont Report
- Boundaries Between Practice and Research

Overview

This chapter examines the history of the Human Subjects Protection System by looking at the major ethical and regulatory bases: Nuremburg Code, Declaration of Helsinki, National Institute of Health's Policies for the Protection of Human Subjects, National Research Act, and the Belmont Report. This chapter further describes the boundaries between practice and research and the basic ethical principles for conducting research.

2.1 Nuremburg Code

Modern human subjects protections began in 1948 with the Nuremburg Code, developed for the Nuremburg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that “the voluntary consent of the human subject is absolutely essential.” Freely given consent to participation in research is thus the cornerstone of ethical

experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable potential risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time. A copy of The Nuremberg Code is provided in Appendix H.

2.2 Declaration of Helsinki

Recommendations similar to the Nuremberg Code were made by the World Medical Association in its Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, and by the 41st World Medical Assembly, Hong Kong, 1989, and by the 52nd World Medical Assembly, Edinburgh, Scotland, 2000 (note of clarification on paragraph 29 added by World Medical Assembly, Washington, DC, 2002). The Declaration of Helsinki further distinguishes therapeutic from non-therapeutic research. A copy of The Declaration of Helsinki is provided in Appendix H.

2.3 NIH Policies for the Protection of Human Subjects

In the United States, regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status NIH's Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the IRB as one mechanism through which human subjects would be protected.

2.4 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects and recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW. The Commission's report set forth the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects which is titled The Belmont Report, and is discussed in depth below.

2.5 Department of Health and Human Services Policy for Protection of Human Research Subjects Common Rule (45 CFR 46)

In 1981, in response to the Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the FDA promulgated significant revisions of their human subjects regulations. The revisions are concerned with some of the details of what the IRB is expected to accomplish and some of the procedures it must follow. The DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. Those "basic" regulations became final on January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991 revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule," as it is sometimes called) was promulgated by the sixteen federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted many of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments that adopt it.

Additional protections for various vulnerable populations have been adopted by DHHS, as follows:

- Subpart B, "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human in Vitro Fertilization" revised effective November, 2001.
- Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" became final on November 16, 1978.
- Subpart D, "Additional Protections for Children Involved as Subjects in Research" became final on March 8, 1983, and was revised for a technical amendment on June 18, 1991.

2.6 FDA 21 PART 50 AND 56

FDA regulations on the protection of human subjects are codified at Title 21 Parts 50 and 56 of the Code of Federal Regulations. Part 50, which sets forth the requirements for informed consent, became final on May 30, 1980, and was revised effective January 27, 1981; March 3, 1989; and June 18, 1991. Subpart C, which provides special protections for prisoners, was adopted on July 7, 1981; the effective date of Subpart C has stayed until further notice. Subpart D, Additional Safeguards for Children in Clinical Investigations, was adopted effective April 24, 2001. Part 56, which sets forth the provisions for institutional review boards, was adopted on January 27, 1981, with revisions to some sections effective February 27, 1981; March 3, 1989; and June 18, 1991.

Additional FDA regulations that are relevant to IRB review of research are Parts 312 (Investigational New Drug Application), 812 (Investigational Device Exemptions) and 860 (Medical Device Classification Procedures).

2.7 Belmont Report

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled *The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research*. The Report sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three essential requirements for the ethical conduct of research involving human subjects. A copy of The Belmont Report is provided in Appendix H.

Respect for Persons

Required by the moral principle of respect for persons (first, that individuals should be treated as autonomous agents, and second that persons with diminished autonomy are entitled to protection), **informed consent** contains three elements: information, comprehension, and voluntariness. First, subjects must be given sufficient information on which to decide whether or not to participate, including the research procedure(s), purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.

Responding to the question of what constitutes adequate information, the Report suggests that a “reasonable volunteer” standard be used: “the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.” Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject’s capacity to understand it; testing to ensure that subjects have understood may be warranted. Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (e.g., minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for such persons may require that the permission of third persons also be given in order to further protect them from harm.

Finally, consent to participate must be voluntarily given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence

Closely related to the principle of beneficence (defined in the Belmont Reports as “persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being”), risk/benefit assessments “are concerned with the probabilities and magnitudes of possible harms and anticipated benefits.” The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of not only the benefits for the individual, but also the societal benefits that might be gained from the research.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the “validity of the presuppositions of the research;” (2) distinguish the “nature, probability and magnitude of risk...with as much clarity as possible;” and (3) “determine whether the investigator’s estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.”

Five basic principles or rules apply when making the potential risk/benefit assessment: (1) “brutal or inhuman treatment of human subjects is never morally justified;” (2) “risks should be minimized, including the avoidance of using human subjects if at all possible;” (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving “significant risk of serious impairment” (e.g., direct benefit to the subject or “manifest voluntariness of the participation”); (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice

The principle of justice mandates that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The “justness” of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (e.g., involving “undesirable” persons in risky research). Further, “social justice” indicates an “order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential

subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.”

Investigators, institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that “arises from social, racial, sexual, and cultural biases institutionalized in society.”

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are “easy to manipulate as a result of their illness or socioeconomic condition.” Care should be taken to avoid overburdening institutionalized persons who “are already burdened in many ways by their infirmities and environments.” Non-therapeutic research that involves risk should use other, less burdened populations, unless the research “directly relate(s) to the specific conditions of the class involved.”

2.8 Boundaries Between Practice and Research

While recognizing that the distinction between research and therapy is often blurred, practice is described as “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals.” The Commission distinguishes research as “designating an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.” The Report recognizes that “experimental” procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such “experimental” procedures should be investigated early, and that institutional oversight mechanisms, such as medical practice committees, can ensure that this need is met by requiring that “major innovation(s) be incorporated into a formal research project.”

Chapter 3: Federalwide Assurance for UNTHSC and its Components

CHAPTER CONTENTS

- Federalwide Assurance (FWA)
- Responsibilities Defined under the FWA
- Investigator Responsibilities
- IRB Committee Responsibilities
- OPHS Staff Responsibilities

Overview

The University of North Texas Health Science Center (UNTHSC) has filed an assurance of compliance called a Federalwide Assurance, with the Office for Human Research Protections (OHRP) in the U.S. Department of Health and Human Services (DHHS). The University is required to enter into this agreement because it receives federal funding for research involving human subjects.

3.1 Federalwide Assurance (FWA)

A Federalwide Assurance (FWA) is a binding written agreement between UNTHSC and OHRP. It states that the University is guided by the ethical principles of the Belmont Report and will comply with 45 Code of Federal Regulations Part 46, or simply 45 CFR 46 for all, not just federally funded, human subjects research. The UNTHSC FWA document is located in Appendix A.

- All human subjects research conducted under the auspices of UNTHSC will be guided by the ethical principals of The Belmont Report.

- The FWA applies to all human subject research in which UNTHSC is engaged, not just federally-funded research.
- The FWA requires compliance with the Federal Policy for Protection of Human Subjects, known as the Common Rule 45 Code of Federal Regulations Part 46, or simply 45 CFR 46.
- The UNTHSC OPHS/IRB has written procedures for reporting unanticipated problems involving risks to subjects or others, serious or continuing noncompliance with federal regulations, or IRB requirements and suspension or termination of IRB approval. UNTHSC must also ensure that a qualified person (or persons) makes the determination regarding research studies that is exempt from IRB review. Finally, UNTHSC IRB has clear, written procedures for conducting IRB initial and continuing review, approving research, reporting IRB findings to the investigator and institution, determining which projects require review more than annually, and how the IRB ensures that changes to ongoing research are reported promptly and are not initiated without IRB review and approval (except when necessary to eliminate apparent immediate hazards to subjects).
- The FWA grants authority to the IRB to approve, require modification in, or disapprove covered human subject research.
- The FWA expects detailed informed consent requirements for research conducted under the auspices of UNTHSC.
- The FWA requires that UNTHSC secure assurances from other institutions participating in collaborative research with UNTHSC investigators when applicable.
- The FWA requires that the University secure written agreements of commitment relevant to human subject protection principles and procedures and UNTHSC IRB oversight if the investigator is not an employee or agent of the University and the IRB agrees to review the research.
- The FWA requires that the University provide the IRB with resources and professional and support staff sufficient to carry out their responsibilities under the assurance.
- The FWA recommends that the Institutional Official, IRB Administrator(s) and IRB Chair(s) complete a training module detailing major responsibilities of these individuals.
- The FWA recommends that the University establish educational training and oversight mechanisms to ensure that research

investigators, IRB members and staff and other appropriate personnel maintain continuing knowledge of, and comply with, relevant ethical principles, relevant federal regulations, OHRP guidance, other applicable guidance, state and local laws and University procedures for the protection of human subjects.

- The FWA details the conditions under which the FWA must be renewed.

3.2 Responsibilities Defined Under the FWA

The Federalwide Assurance also describes the responsibilities of the Institution, the Designated Institutional Official, the Institutional Review Board and the investigator, which are detailed below. All investigators at UNTHSC are expected to conduct research in accordance with the provisions of the Federalwide Assurance and ensure that the rights and welfare of the individuals involved are protected.

Faculty members who assign or supervise research conducted by students have an obligation to carefully oversee the research to ensure that students adequately safeguard the rights and welfare of subjects.

3.3 Investigator Responsibilities

“The Principal Investigator is Responsible for Everything.”

This simple but broadly encompassing statement demonstrates that the Principal Investigator (PI) on a research project involving human subjects is responsible for acquiring the appropriate knowledge regarding human subject protections, ethics, federal regulations, training, and monitoring to conduct his/her proposed research. The PI must assure that his/her key study personnel are adequately trained and knowledgeable regarding human subject protections, ethical considerations, and federal regulations applicable to the proposed research. The PI is responsible for complying with the training, monitoring, and human subject research guidance as outlined in the Assurance and the OPHS-IRB Manual. More details on PI responsibilities are described in Chapter 8.

3.4 IRB Committee Responsibilities

The IRB Committee is to review all research activities and document its findings regarding ethical considerations, scientific merit, adherence to federal regulations and IRB principles and procedures. The IRB Committee must review and monitor ongoing research for adherence to the Federal regulations and IRB principles and procedures. See Chapter 4 for more details on IRB activities and duties.

3.5 OPHS Staff Responsibilities

The OPHS staff will participate in ongoing auditing and monitoring activities to assure adherence to the federal regulations. They will also participate in the revisions of the OPHS-IRB Manual as applicable. Further, all information provided under the Federalwide Assurance must be updated at least every 36 months, even if no changes have occurred in order to maintain an active Assurance approved by OHRP. Amendments to the Assurance are to be reported promptly to OHRP. This includes changes to IRB Committee rosters and the addition or deletion of an IRB Chair or legally recognized entity of UNTHSC. UNTHSC will maintain principles and procedures reflecting the current practices of the IRB in conducting reviews and approvals under its Assurance. These principles and procedures will be maintained and kept current by the UNTHSC OPHS. They will be reviewed at least every 36 months. All revision dates will be listed under the revision date for each principle and procedure. Changes in principles or procedures are to be determined by the appropriate OPHS or University official. As appropriate, principles and procedures are developed, revised and approved by the VP for Research, the Director of OPHS, and the IRB Chair.

Annually, the OPHS budget will be reviewed by the Director of OPHS and the VP for Research and modified, as necessary, to accommodate the volume and type of research reviewed, education, space, facilities, and staff.

Chapter 4: UNTHSC Institutional Review Board (IRB)

CHAPTER CONTENTS

- Brief Description of the IRB
- Membership of the IRB
- IRB Member Requirements
- IRB Use of Consultants
- IRB Support Staff (OPHS)
- IRB Liaisons (Departmental)
- IRB Chairs and Vice Chairs
- IRB Voting Requirements
- IRB Records
- Development, Approval, and Maintenance of The OPHS-IRB Manual

4.1 Brief Description of the UNTHSC IRB

This chapter explains the membership of the IRB, the roles and requirements of IRB members, Chair, Vice-Chairs, and reviewers for the Institutional Review Board at the University of North Texas Health Science Center (UNTHSC), also referred to as “the Institution,” and “the University.” Additionally, this chapter explains the use of consultants, the role of OPHS staff, voting requirements, and various requirements for IRB records.

At this time, there is only one (1) Institutional Review Board at the University of North Texas Health Science Center. * This IRB reviews and approves research in accordance with Department of Health and Human Services (DHHS) regulations in 45 CFR 46, and in accordance with Food and Drug Administration (FDA) requirements set forth in 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812. In addition, the IRB complies with HIPAA and its

regulations set forth in 45 CFR 160 and 164 and Texas law as it pertains to human subjects research.

* Note: In the future, additional IRBs may be required for protocol review as research operations expand. In the event that new IRBs are formed, the same principals and procedures will apply to those IRBs except where specifically noted in their formation charter.

4.2 The Membership of the IRB Committee: Number, Qualifications and Diversity of Members

The IRB shall have a minimum of nine, but generally between thirteen (13) and fifteen (15) members with varying backgrounds to adequately review the research activities commonly conducted by the Institution. Major clinical and basic science departments are represented to provide the experience and expertise sufficient for review of the research activities conducted at the Institution. There shall be at least one member whose primary concerns is in non-scientific areas, and one member who is otherwise not affiliated with the Institution (either as an employee or student) and is not part of the immediate family of a person who is affiliated with the Institution.

To enable the IRB to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice, the IRB shall include persons knowledgeable in these areas and may include representatives of administration.

The IRB is sufficiently qualified through the experience, expertise and diversity of its members – including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes – to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

Because the IRB may review research that involves a vulnerable category of subjects (children, pregnant women, prisoners, and handicapped or mentally disabled persons), each IRB shall involve the input and advice – as members or consultants as appropriate – of persons who are knowledgeable about, and experienced in, working with these categories of subjects.

Every effort will be made to ensure that each IRB does not consist entirely of one gender – so long as no selection is made to the IRB on the basis of gender.

Alternate Members

When deemed necessary by the IRB Chair, and when requested by Department Chairs or Deans, a regular IRB member may have an alternate appointed for that IRB member. Formally appointed alternate IRB members may represent IRB members, provided the alternate's qualifications are comparable to the primary member to be replaced. The IRB membership rosters identify the primary member(s) for whom each alternate member may substitute.

Note that *ad hoc* substitutes are not permissible as members of the IRB.

Prior to the IRB meeting, materials required for review are sent to the alternate member. The IRB minutes document when an alternate member replaces a primary member. When alternate substitutes for a primary member, the alternate member must receive and review the same material that the primary member received or would have received.

Members and their alternates count as only one voting member, and therefore may not vote concurrently. Alternates are not counted as “members” in establishing the numerical quorum of the IRB, except when they substitute for members during the IRB meeting.

Alternates are invited to attend all IRB meetings, whether they are eligible to participate as voting members or not, in order to assure familiarity with the IRB practices.

Ex-Officio Guest Observers

Ex-officio guests and observers may attend IRB meetings, depending on the relevance/need to be in attendance. As such, ex-officio participants in IRB meetings and activities function as observers and consultants only, and are not members of the IRB and thus do not vote on the IRB. Their presence or absence has no effect on quorum (see below).

4.3 IRB Member Requirements

Selection and Appointment

For the broadest possible slate of candidates to serve on the UNTHSC IRB, nominations are considered from a wide range of sources. Members of the IRB may be recommended for appointment by current IRB members, OPHS staff, Deans or Department Chairs. Non-affiliate members not associated with the Institution are identified by interest and relevance and recommended for appointment by members of the IRB, IRB staff, Departments or Schools. Self-nominations are also encouraged.

The Director of OPHS will meet with identified candidates to discuss tasks, responsibilities and answer questions. And when possible, interested persons are encouraged to attend an IRB meeting as an observer.

Nominations for membership are then submitted, in writing, to the Institutional Official (VP for Research) who will make the formal appointment.

IRB committee membership lists can be found in Appendix G and on the OPHS-IRB website at: <http://www.hsc.unt.edu/Sites/OPHS-IRB/Documents/IRB%20Members.pdf>

Length of Service

Appointments to the IRBs are for a period of 3 years, but may be extended, on a year-by-year basis, in order to provide continuity in representation. Membership of the IRB and the

qualifications of the IRB members are reviewed on an annual basis. Continued tenure on the IRB is at the discretion of the Chair of the IRB and the VP for Research upon advisement from the Director of OPHS. For more information, see the “Evaluation of IRB Members” section located further in this chapter.

Duties

Members of the IRB are required to:

1. Attend a minimum of 75% of the convened IRB meetings;
2. Review the IRB application and informed consent form for all research proposals assigned;
3. Conduct Expedited Reviews as assigned by the Chair and/or Director OPHS;
4. Review and promptly inform the Chair of corrections or additions to convened board meeting minutes.

Attendance Requirements

IRB members are required to attend a minimum of 75% of convened meetings. If a member is unable to attend a meeting, the IRB office must be informed, sufficiently in advance, to assure an appropriate number and composition of Board members to be in attendance for that meeting. Frequent absences among non-affiliated members are not acceptable.

Member Removal

Members serve at the discretion of the Chair and/or institutional official. Members who are not in regular attendance – or who, in the discretion of the Chair and/or Institutional Official, should not serve as IRB members – will be removed from the IRB.

Liability for IRB Members

IRB members fulfill their administrative and institutional service responsibilities to the University, in part, by serving on an IRB committee. Accordingly, the University will indemnify IRB members in the event of a legal dispute relating to the actions of the committee, provided that the IRB member has acted in good faith and in accordance with federal requirements, state and local laws and University policy.

Training of the Chair, Vice Chairs and Members

The Chair and Vice Chairs of the IRBs are trained via their attendance at appropriate IRB training conferences, courses and meetings (including PRIM&R conferences) and membership on the IRB. IRB members are initially trained as guests (observers with nonvoting capacity) of the IRBs, and they also attend appropriate courses as well as local or national meetings (including PRIM&R conferences). Ongoing education of the IRB

membership includes distribution, review and discussion at IRB meetings of relevant publications (such as “IRB: A Review of Human Subjects Research, reprints of relevant journal articles, and publications and materials from relevant federal agencies, as well as periodic review by the Chair or Vice Chairs.

IRB members are required to complete the IRB Protection of Human Subjects education sessions available online through the CITI website: <https://www.citiprogram.org/default.asp>

Member Conflict of Interest Policy

Conflict of Interest policy considerations apply to IRB members. The term “Conflict of Interest” in this manual refers to situations in which financial or other personal considerations compromise – or have the appearance of directly and significantly compromising – an individual’s professional judgments in proposing, conducting, reviewing or reporting research. The bias caused by such conflicts may affect collection, analysis, and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, involvement of human participants, and the use of statistical methods.

The IRB is not in a position to adequately verify attestations of conflicts of interest. In lieu of substantiation, the expectation for conflict of interest disclosure is presented below. Unless information is indicated to the contrary, the authenticity of the IRB members disclosure is based on trust, candor and personal attestation.

For studies reviewed by the full board, at the beginning of every meeting, the IRB Chair or Vice Chair asks if any of the members has a Conflict of Interest. If they do, they are asked to recuse themselves (be absent from the meeting room before the final discussion and vote, except when requested by the IRB to be present to provide information) from the meeting while the study with which they have a Conflict of Interest is reviewed. For studies reviewed in an expedited manner, the reviewers are expected to indicate to the IRB Chair or Vice Chair that they have a Conflict of Interest with regards to the study that they have been asked to review. The IRB prohibits the participation in IRB initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

An IRB member is considered to have a Conflict of Interest if:

- The IRB member or a Close Relation of the IRB member (spouse, mutual financial dependent, significant other, or person in an intimate relationship, child, parent, or sibling (including in-laws and step-relations), grandparent, grandchild, niece or nephew, aunt or uncle, or cousin) is involved in the conduct of the research;
- When the IRB or Close Relation of the IRB member has a supervisory, managerial or ownership interest in the research sponsor, or licensee, or a company having an economic interest in the research;

- Equity interest held by an IRB or Close Relation of an IRB member in a research sponsor, or licensee, or in any company having an economic interest in the research;
- Incentive payments, bonus payments or finders fees relating to the proposal paid to the IRB member or Close Relation;
- Consultation arrangements between the IRB member or Close Relation of an IRB member and an organization or individual having an economic interest in the research, which, when aggregated for the IRB member and the Close Relations of the IRB member, exceeds \$10,000;
- Gifts, gratuities, or special favors from the sponsor, which, when aggregated for the IRB member and the Close Relations of the IRB member, exceeds \$10,000;
- Honoraria, travel expenses reimbursement, or other reimbursements from the sponsor, which, when aggregated for the IRB member and the Close Relations of the IRB member, exceeds \$10,000;
- Intellectual property rights related to the research IRB member and the Close Relations of the IRB member.
- The University of North Texas Health Science Center Conflict of Interest policies can be found in Chapter 8.6, in Appendix C, and on the OPHS website at the following link:
http://www.hsc.unt.edu/sites/OPHSIRB/Documents/Conflict_of_Interest.pdf

Evaluation of IRB Members

The IRB members will be evaluated annually by the IRB Chair and OPHS staff using the evaluation tool below. The members will be evaluated based on experience, expertise, diversity, contributions at the IRB meetings, knowledge of the IRB process, training, attendance at the meetings, and other contributions to the IRB. If a member is found to be deficient in a particular area or areas, they will either be further evaluated, or in some cases they may be replaced or asked to resign from the IRB. The IRB Chairs are evaluated by the Director of OPHS in consultation with the President on an annual basis.

IRB Member Evaluation Tool

IRB Member Qualifications

Experience, Expertise and Diversity

- Below-In reviews, shows minimal sensitivity towards race, gender, and cultural backgrounds

- Meets-In reviews, shows some sensitivity towards race, gender, and cultural backgrounds
- Exceeds-In reviews, is sensitive to race, gender, cultural backgrounds, and community attitudes

Contributions at IRB Meetings

- Below-Participates occasionally
- Meets-Participation includes thoughts and comments on various topics
- Exceeds-Contributes thoughtful and meaningful comments to the discussions

Knowledge of IRB Process

- Below-Knows the basics of the IRB process
- Meets-Knows most of the IRB process
- Exceeds-Articulate and informed on the current IRB process

Attendance

- Below-Attends some scheduled
- Meets-Attends most scheduled meetings
- Exceeds-Attends all scheduled meetings

4.4 IRB Use of Consultants

The OPHS, on behalf of the IRB, may in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond, or in addition to, that available on the IRB. These consultants are not counted as “members” in establishing the numerical quorum for the IRB and may not vote with the IRB. An honorarium may be provided at the discretion of the IRB Chair and/or the Director of OPHS. If it is determined that a consultant is needed for the review of a protocol, the IRB Chair or Director of OPHS will ask the IRB members and colleagues to refer them to individuals that would have experience with the specific type of research being reviewed. The consultants will be provided with the same information that the other IRB members receive. The IRB member Conflict of Interest policy also applies to consultants. The IRB Chair or Director of OPHS will be responsible for providing the consultant with a copy of the IRB member Conflict of Interest policy prior to their review of the study. Once the consultant has read the policy, the consultant will be asked if a conflict exists. If answered in the affirmative, the consultant may

not review the study. All consultants are required to maintain confidentiality and are notified of this prior to reviewing proposed research for the IRB.

Copies of the consultant review are supplied to the IRB members. Consultant(s) may be asked to attend the meeting for further clarification, if deemed necessary by the IRB Chair or OPHS. Key information from the consultant will be included in the IRB meeting minutes and a copy of all documentation will be kept in the study file.

4.5 IRB Support Staff via OPHS

The OPHS is, in part, the support staff for the IRB and assists the Chair and Vice Chairs in IRB activities. Among other duties, OPHS staff is responsible for submitting written notice to investigators and the Institution regarding IRB actions.

OPHS staff are hired after consultation between senior IRB individuals such as: IRB Chair and/or the Director of OPHS. OPHS staff members are trained by the Director and other staff of OPHS, with assistance from the IRB Chair and IRB members as needed. This training includes taking the CITI education courses, reading of the federal, state, and local regulations, and review of the OPHS-IRB Manual. A Bachelor's Degree (or equivalent) is required, prior IRB experience is desirable, and training is provided. Master's Degree in a biomedical, social science, or behavioral field is preferred. OPHS staff are encouraged to become Certified IRB Professionals (CIPs). Annual reviews of OPHS staff are conducted by the Director of OPHS in consultation with the IRB Chair. The following criteria: knowledge of the IRB process and regulations, continuing training, work attendance, and, overall ability to function as an asset to the IRB, will be measured. If a staff member is found to be deficient in a particular area or areas, they will be further educated. If gross errors have been uncovered, further actions, as described in University policies, will be taken.

4.6 OPHS-IRB Departmental Liaisons

In those departments with significant numbers of faculty, staff, or students regularly engaged in human subjects, it is desirable to identify and involve Departmental OPHS-IRB Liaison personnel. These persons, trained by OPHS will assist with timely review and preparation of protocols prior to their submission to the OPHS for review by the IRB. It is hoped that such "in-house" liaisons will enhance and support awareness and compliance among the various investigators within that department while at the same time promoting sound ethical and practical human research activities campus-wide.

4.7 IRB Chairs and Vice Chairs

Chairperson

Selection and Appointment

The Chair is selected from among the faculty of the Institution and appointed by the Institutional Official. The Chair must previously have served as a member of an IRB, either at UNTHSC or in another institution.

Selection Criteria

The criteria used to select a Chair include experience with, and knowledge of, applicable federal regulations, state laws, and Institutional policies. The candidate must be willing to commit to the IRB; must have past experience as an IRB member; and they must demonstrate excellent communication skills, along with an understanding basic science, applied science, social/behavioral science, and clinical research. They must also be flexible and demonstrate a thorough understanding of ethical issues involved in human subject research.

Length of Term/Service

The term of appointment of the Chair is determined by the Institutional Official in consultation with the Director of the Office for the Protection of Human Subjects.

Attendance Requirements

The Chair is expected to attend all convened IRB meetings and be available to OPHS staff on an as-needed basis for related IRB and human research protection program duties.

Duties

The Chair of the IRB convenes and chairs the meetings of the IRB. The Chair may conduct or delegate expedited review of research that qualifies for such review, review the responses of investigators to stipulation and contingencies of the IRB (to secure IRB approval) and review and approve minor changes in previously approved research during the period covered by the original approval. The Chair may delegate such authority to authorized Vice Chairs, or the Director of OPHS, as needed.

Vice Chairpersons

Selection and Appointment

Where possible, the Director of OPHS also serves as the Chair or Vice Chair of the IRB. This appointment allows for continuity and efficiency in managing Exempt, Expedited and Full Board reviews and assignments. The Vice Chairs are formally appointed to the IRB by the Institutional Official (the UNTHSC Vice President for Research). Additional Vice Chairs may

also be appointed by the Institutional Official as needed and must have previously served as members of an IRB, either at UNTHSC or at another institution.

During a convened meeting, when regularly appointed Vice Chair(s) are absent, the IRB Chair may designate an IRB member present at that meeting to serve in a transitional interim appointment as Acting IRB Chair, such appointment lasting until the IRB Chair rescinds the interim appointment.

Length of Service

The term of appointment of the Vice Chair is the same as for the IRB Chair (3 years).

Attendance Requirements

The Vice Chair is required to attend the majority of convened IRB meetings.

Duties

The Vice Chair of the IRB is authorized to carry out expedited review of research that qualifies for such review. The Vice Chair shall be authorized by the Chair to review the responses of investigators to contingencies of the IRB (to secure IRB approval) and to review minor changes in previously approved research during the period covered by the original approval. In addition, the Vice Chair assumes the Chair's duties in the Chair's absence or in the case where the Chair must recuse him/herself due to a conflict of interest.

4.8 IRB Voting Requirements

Reviews of proposed research are conducted at a convened IRB meeting at which a majority of the members are present. At least one member whose primary concerns are in non-scientific areas, at least one member whose primary concerns are in scientific areas, and one non-affiliated member (so-called community member) must be present. In the event a majority of members are not present, or there is no member whose primary concerns are non-scientific, or a non-affiliated member is not present, the meeting will not be called to order (or if any of these circumstances arises after the meeting has been called to order, it will be adjourned) and will be rescheduled. The OPHS staff will monitor the members that are present at the meeting and determine that the meetings are appropriately convened and remain so.

In order for the research to be approved at the convened meeting it must receive the approval of a majority of the voting members present at the meeting.

The IRB may, in its discretion, invite individuals with competence in special areas (consultants) to assist in the review of complex issues requiring expertise beyond, or in addition to, expertise of the IRB members. These consultants may not vote with the IRB.

Votes submitted prior to a convened meeting by mail, telephone, fax or e-mail are not permissible. However, pre-meeting comments of the absent members may be submitted and considered by the attending IRB members.

There is a prohibition against the voting and participation of a member in the IRBs' initial or continuing review of any project in which that member has a conflicting interest, except to provide information requested by the IRB.

Recused members do not count towards a quorum.

Note that only IRB members listed as members on the official federal Office for Human Research Protections (OHRP) IRB roster may vote at a convened meeting.

4.9 IRB Records

IRB Membership Roster

The OPHS maintains rosters of IRB membership including: name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the Institution. Changes to the IRB membership roster are reported to OHRP by the OPHS Director.

Written Procedures and Guidelines

The IRB maintains written procedures as required by 46 CFR 46.103(b)(4), (5). These documents are developed and maintained by OPHS staff who attend every convened meeting of the IRB as non-voting participants of Board meetings.

Meeting Minutes

IRB meeting minutes are recorded in sufficient detail to show attendance at the meetings (including number of votes for each action during the meeting), members present and any consultants/guests/others are listed separately.

The IRB meeting minutes include:

1. Summary of discussion of protocols and relevant issues (if any) and their resolution;
2. Record of IRB decisions (actions taken by the IRB);
3. Record of voting (including the number of members voting for, against, abstaining and recusal) for each action;

4. The basis for requiring changes in approving, disapproving, or deferring research;
5. Names of IRB member(s) recused and not present during the discussion or vote in any research protocol under review and of those who abstain;
6. Description of the materials reviewed for both new and continuing review proposals. Such materials may include the IRB application, clinical protocol, investigators brochure, informed consent form documents, continuing review form, primary reviewer's evaluation (for continuing review) and any other materials submitted for review;
7. All applicable waivers are discussed and documented (with justification) in the IRB minutes including, waiver or alteration of informed consent and written informed consent;
8. Protocol specific determinations on studies involving vulnerable populations (45CFR46 Subparts B, C, D) are documented and justified according to the regulations ;
9. Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the informed consent document;
10. Approval period for initial and continuing reviews;
11. Rationale for significant risk/non-significant risk device determinations;
12. If an IRB member has a Conflict of Interest regarding a study being reviewed, they will recuse themselves from the review of the study. The name and reason for absence will be included in the minutes.

Minutes from each IRB meeting are distributed to all IRB members and to the VP for Research for review according to the Federalwide Assurance and appropriate committees. IRB members are required to review the minutes and note any corrections or additions at the first meeting following distribution of the minutes.

Records Retained in the IRB Files

Research Project Protocols, including Amendments/Revisions include each of the following (as relevant):

- Initial Application;
- Approved sample consent documents;
- Clinical protocol, including amendments/revisions;

- Investigators brochure(s);
- Grant application(s);
- Scientific evaluations, if any, that accompany the proposals;
- Any supporting information that accompany the studies;
- Category of approval for exempt, expedited, full board (when necessary), and continuing review submissions;
- Progress reports submitted by investigators;
- All continuing review activities;
- Serious/Unanticipated Adverse Event (SAE) Reports;
- Statements of significant new findings provided to subjects;
- Approval period (for new and continuing submissions);
- Conflict of Interest Forms (Expedited and Full Board studies);
- Verification of training in the protection of human subjects for key personnel (e.g. CITI training certificates);
- Curriculum Vitae (CV) of the Principal Investigator;
- All related correspondence and “notes to file.”

Communications to and from the IRB

Copies of all correspondence between the IRB, the OPHS and investigators are maintained in central OPHS files.

Adverse Event Reports

Adverse Events reports are retained in the central OPHS files.

Records of Continuing Review

Copies of all progress reports and continuing review are maintained in central OPHS files.

Record Retention Requirements for IRB

Study documents and/or records acquired by the IRB shall be retained according to the terms of federal regulation, either electronically or as hard copy. Per federal regulations (*45 CFR*

46.115(b) and 21 CFR 56.115(b)), the OPHS / IRB shall be responsible for maintaining its documentation, files and IRB meeting minutes relevant for each study for a minimum of three (3) years following IRB approval of the closure of the study. In accordance with federal HIPAA regulations, IRB records pertaining to records containing protected health information (PHI) are retained for at least six years.

Emergency Use Reports

Copies of all Emergency Use Reports are maintained in central OPHS files.

Access to Files

OPHS and IRB records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

4.10 Confidentiality Requirements for IRB members, Consultants, Advisors, Observers

IRB members and OPHS staff will have access to a wide array of information of a sensitive, personal, financial and confidential nature. In order to maintain the confidentiality of information received and reviewed by the OPHS and/or the IRB, the following standards of conduct and procedures will apply:

- a) IRB members (including alternates), OPHS staff, consultants, *ex officio* personnel serving on IRB-related tasks, as well as observers/guests attending IRB meetings or discussion will not discuss or divulge any information beyond what is required to fulfill their obligation to protect human subjects or to remain compliant with applicable law. Further, IRB members (including alternates), OPHS staff, consultants, *ex officio* personnel serving on IRB-related tasks, as well as observers/guests attending IRB meetings or discussion will not discuss, disclose or reproduce IRB or OPHS documents or information except as required by regulations, these principals and procedures, OPHS processes and actions, or as otherwise required by law.
- b) Each IRB member (including alternates), OPHS staff member, any consultant serving on IRB-related tasks, as well as any observers/guests attending IRB meetings or discussion will sign and honor a Confidentiality Agreement at the time of joining the Board, OPHS or becoming involved with IRB activities or discussions. This Confidentiality Agreement will be kept in an appropriate file located within OPHS.
- c) Because confidentiality is essential to the smooth operation of a human research protection program, breach of these confidentiality requirements may result in one or more of the following:

- Removal from membership on the IRB

- Exclusion from future IRB activities and/or access to OPHS or IRB documents
 - Referral to appropriate UNTHSC official(s) or committee(s) for further action if warranted
- d) This Confidentiality Agreement and requirement continues indefinitely, even after the end of any affiliation with the University of North Texas Health Science Center.

4.11 Development, Approval, and Maintenance of the OPHS-IRB Manual

The UNTHSC IRB's principals and procedures for the review of research activities under its jurisdiction are written and implemented according to federal regulations, state and local laws, University policies and procedures, and standards of regulatory, accrediting, and funding agencies. To assure continued compliance, the following will be conducted:

- The OPHS-IRB Manual is to be reviewed every three years and when changes in regulations, laws, and institutional policies necessitate revision;
- The OPHS is charged with the appropriate implementation and enforcement of human research protection program policies and procedures consistent with other University policies and procedures.

Investigator Responsibilities

The investigator will review the OPHS-IRB Manual as part of the required initial training for conducting human subjects' research at the University. The current manual is located on the OPHS-IRB website at: <http://www.hsc.unt.edu/sites/ophs-irb/>

It is the responsibility of the investigator to routinely view the IRB website for new or revised IRB principles and procedures. The investigator will contact IRB staff for clarification of principles and procedures, when necessary. All investigators and key personnel are required to take CITI training (see Chapter 8.2 Investigator's Role and Responsibility-Educational Requirements).

OPHS Administration Responsibilities

OPHS staff will routinely view the OHRP and FDA websites for issuance of guidance documents, changes in regulations, and determination letters. The OPHS is responsible for the development and maintenance of the OPHS-IRB Manual as guided by the Director of the Office for the Protection for Human Subjects.

The Director of OPHS will contact the Office of General Counsel and Office of Compliance, when necessary, to discuss changes and assist in the interpretation of federal, state and local

regulations affecting IRB principles and procedures. The Office for the Protection of Human Subjects staff will provide educational sessions to the IRB members and university research staff regarding IRB principles and procedures, as well as updates or revisions.

OPHS Staff Responsibilities

The OPHS staff will use the OPHS-IRB Manual posted on the OPHS-IRB website when reviewing IRB applications. The OPHS staff may consult with other personnel for guidance in applying the IRB principles and procedures. If the OPHS staff notices that a principle or procedure is inaccurate or out of date, he/she should bring it to the attention of the OPHS Director. It is the responsibility of all OPHS staff to keep the OPHS-IRB Manual current and applicable to the daily processes of the university's human research protection program and to follow the principles and procedures as stated.

Chapter 5: IRB Review and Types of Submissions

CHAPTER CONTENTS

A. What Requires IRB Review

This chapter describes what human subjects research is and provides a definition for research and human subject. If a research activity is determined to be human subjects research, it must be reviewed and approved by the UNTHSC IRB before the proposed research activity is initiated. All human subjects research must be reviewed by the IRB if:

- The research is sponsored by UNTHSC or an external funding source;
- The research is conducted by or under the direction of any employee or agent of UNTHSC (including students) in connection with their institutional responsibilities;
- The research is conducted by or under the direction of any UNTHSC employee, agent, faculty, staff, or student using any property or facility of UNTHSC; or
- The research involves the use of UNTHSC's non-public information to identify or contact human subjects.

Thus, all research involving human subjects conducted by any UNTHSC employee, student, faculty or staff, no matter where it is conducted (on or off campus), must be reviewed and approved by the UNTHSC OPHS and the UNTHSC IRB as required by these principles and procedures and federal regulations.

In special situations, UNTHSC may authorize review by another IRB that is listed under the UNTHSC FWA through an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Authorization Agreement signed by the UNTHSC Institutional Official and in accordance with the special terms of that Authorization Agreement.

UNTHSC adheres to the Department of Health and Human Services (HHS) regulations Title 45 part 46, Food and Drug Administration (FDA) regulations 21 CFR 50 and 21 CFR 56, as well as all state and local regulations regarding human subjects research.

B. Types of IRB Submissions

All UNTHSC human subjects research projects must undergo review and approval by the OPHS, and if needed, the IRB, prior to initiating research activities. This chapter provides an inventory of common submissions that an investigator may send to the OPHS. It is provided as a frame of reference and discusses possible levels of review for each submission but should not be used to determine the level of review. This chapter contains information on the following types of submissions:

- Not Human Subjects Research submissions
- Exempt submissions
- New submissions (non-exempt protocols: full, expedited, facilitated review)
- Applications lacking definite plans for involvement of human subjects
- Continuing reviews (full, expedited, facilitated review)
- Expired protocols (subject protections needing approval for continued treatment, reactivation)
- Amendments (full, expedited, and facilitated)
- Adverse event reports
- Relevant new information
- Investigator responses to IRB correspondence

C. Levels of IRB Review

- Exempt Human Subjects Research
- Expedited Review
- Full Board Review
- Appeals Process of IRB Determination

- Length of Protocol Approval
- IRB Review of Scientific Merit

This chapter gives an overview of the three levels of review found in the “Common Rule” (45 CFR 46) and review procedures for each. The levels of IRB review are applied to initial review of the project or activity, revisions or amendments, and continuing review. The levels are:

- Exempt review (protocols involving minimal risk and falling within one of six defined categories); and
- Expedited review (protocols involving no more than minimal risk and falling within one of nine defined categories); and
- Full board review (protocols involving greater than minimal risk)

Certain studies may have the characteristics of human subject research but may not meet the regulatory definition. At UNTHSC, these studies are considered Not Human Subjects Research (NHSR) because they do not meet the federal definitions of human subjects and/or research. Any investigator who is unsure of whether their proposal constitutes “human subject research” should contact OPHS for guidance. OPHS staff will determine if the study is human subject research based on the methodology, the subjects involved, whether identifiers will be collected and stored, how the information will be used, and risks to the subjects. UNTHSC policy does not allow investigators to make this determination themselves. If a study does not qualify as human subject research, OPHS will issue a letter stating the project does not require IRB review or approval.

5.1 Helpful Definitions

Research

The Department of Health and Human Services (HHS), in Title 45 part 46, defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Activities that meet this definition constitute research for purposes of this 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.

Human Subject

HHS in Title 45 part 46, defines a human subject 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.

The FDA in Title 21 part 50.3, defines a human subject as “an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.”

Intervention, Interaction, and Private Information

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

Since the definition of a human subject is a "living" individual, research involving autopsy materials or cadavers may not be considered human subjects research and may not require review by the IRB. However the activity may be subject to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Contact the OPHS office if there are any questions on either topic.

Clinical Investigation

The FDA, in Title 21 part 50.3, defines a clinical investigation as “any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding non-clinical laboratory studies.”

Note: Sections 505(i) and 520(g) refer to any use of a drug other than the use of an approved drug in the course of medical practice and 520(g) refers to any use of a medical device other than the use of an approved medical device in the course of medical practice.

Human Subjects Research

Any activity that either meets the HHS definition of both research and human subjects or meets the FDA definition for both research and human subjects is human subjects research.

Engagement in Research

The OPHS defines engagement in research according to OHRP's 1999 guidance on the engagement of institutions in research. An institution becomes "engaged" in human subjects research when its employees or agents (all individuals performing institutionally-designated activities or exercising institutionally-delegated authority or responsibility, including faculty and students):

- (i) Intervene or interact with living individuals for research purposes: or
- (ii) Obtain individually identifiable private information for research purposes

[45 CFR 46.102(d),(f)].

An institution is automatically considered to be "engaged" in human subjects research whenever it receives a direct HHS award to support such research. In such cases the awardee's institution bears ultimate responsibility for protecting human subjects under the award.

IMPORTANT NOTE: UNTHSC requires review by the UNTHSC IRB if the institution is "engaged" in research regardless of funding. If another institution is also "engaged" in the research, they may also require an IRB review as well.

5.2 How to Determine if the Research Project Requires Human Subject Review

HHS, in Title 45 part 46, defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Certain activities have the characteristics of research but do not meet the regulatory definition of human subjects research needing OPHS-IRB review. There are three categories of research to be considered:

1. Definitely human subjects research;
2. A gray area that may or may not be considered human subjects research; and
3. Studies that do not qualify as human subjects research.

Any individual who is unsure whether or not a proposed activity constitutes "human subjects research" should contact OPHS for guidance. OPHS staff and/or the IRB Chair and/or Vice

Chairs will determine whether a given research project is subject to 45 CFR 46, 21 CFR 50, 56 and any other requirements dictated by a sponsor.

Note that ALL studies involving human subjects require a formal evaluation by the OPHS acting on behalf of the IRB. Given the ever-changing pace and complexity of regulations, faculty, staff and students are encouraged to work closely with OPHS staff to determine if their research project requires review by the IRB.

If, after proper evaluation, it is determined that the research study does NOT require review by the IRB, OPHS can issue a letter, if requested by the investigator, stating that the study does not qualify as human subjects research and therefore does not need to be reviewed and/or approved by the IRB.

Some examples of research that may **not** require IRB review include:

- Data collection for internal departmental, school, or other University administrative purposes (e.g. teaching evaluations, “customer service” surveys).
- Surveys issued or completed by University personnel for the intent and purposes of improving services and programs of the University or for developing new services or programs for students, employees, or alumni, as long as the privacy of the subjects is protected, the confidentiality of individual responses is maintained, and survey participation is voluntary. This would include surveys by professional societies or university consortia.

Note: If at a future date, an opportunity arose to contribute previously collected identifiable or coded survey data to a new project producing generalizable knowledge, application for IRB review will be required before the data could be released to the new project. Contact the OPHS for further guidance.

- Fact-collecting interviews of individuals where questions focus on things, products, or policies, rather than on people or their experiences. Example: canvassing librarians about inter-library loan policies or rising journal costs.
- Course-related activities designed specifically for educational or teaching purposes, where data is collected from and about human subjects as part of a class exercise or assignment that is not intended for use outside of the classroom.
- Instruction on research methods.

Note: If the classroom research is more than minimal risk or involves vulnerable populations, it must be submitted to the IRB. Instructors of research courses are encouraged to consult with OPHS staff.

- Searches of existing literature.
- Research involving a living individual, such as a biography, that is not generalizable beyond that individual.
- Procedures carried out under independent contract for an external agency. Examples include personnel studies, cost-benefit analyses, customer satisfaction studies, biological sample processing.
- Research involving deceased individuals (i.e. where the person previously promised their body for research, a person died during the research, etc.)

Note: Some research in this category may need OPHS and/or IRB review. Please contact the OPHS for further information.

- Research about things or expertise, rather than “about whom” (questions not about the individual providing the information).
- Quality Improvement - In general, quality improvement projects are not considered research unless there is a clear intent to use the data derived from the project to improve the quality of patient care or efficiency of a healthcare operation and also contribute to generalizable knowledge via publication in professional journals and/or presentation at national or regional meetings. Any individual who is unsure whether or not a proposed quality improvement project should be classified as research should contact the IRB for guidance. If a quality improvement project is completed (i.e., all the data is collected, analyzed, and conclusions have been drawn) and the decision is made to publish or present the data, it is not research providing no further analysis is required to test a hypothesis for the purpose of publication or presentation. On the other hand, if it is necessary to reexamine or reanalyze the data derived from the quality improvement project, the activity now constitutes research. Depending on whether or not subject identifiers are maintained, it may qualify as not human subjects research.
- Case histories which are published and/or presented at national or regional meetings are not considered research if the case is limited to a description of the clinical features and/or outcome of a single patient.
- Research projects that involve the use of publicly available data to analyze public figures do not require IRB review.
- Specimens and Data Sets (Secondary Data Analysis) – If the data set used contains no identifiers (either direct or link code numbers) the projects are not human subjects research. If the data set contains

identifiers, and contains no private information (information about behavior that occurred in a context in which the individual could reasonably expect that no observation was taking place or involves no information which had been provided for specific purposes for which the individual could reasonably expect would not be made public), the project is not human subjects research.

- Research with unidentified specimens from other institutions is not human subjects research (see Section 13.7 on Specimens and OHRP Guidance).

For additional information refer to Chart 1 of the Human Subject Regulations Decision Charts (see Appendix E).

Types of IRB Submissions

All UNTHSC human subjects research projects must undergo review and approval by the OPHS, and if needed, the IRB, prior to initiating research activities. Common submissions that an investigator may send to the OPHS include:

- Not Human Subjects Research submissions
- Exempt submissions
- New submissions (non-exempt protocols: full, expedited, facilitated review)
- Applications lacking definite plans for involvement of human subjects
- Continuing reviews (full, expedited, facilitated review)
- Expired protocols (subject protections needing approval for continued treatment, reactivation)
- Amendments (full, expedited, and facilitated)
- Adverse event reports
- Relevant new information
- Investigator responses to IRB correspondence

Review Levels for New Submissions:

Protocols are submitted to OPHS for pre-review assignment for appropriate human subject review. At this stage, OPHS staff evaluate the protocol and assign it to one of the following review categories:

1. Exempt
2. Expedited
3. Full Board

5.3 Exempt Submissions

Various minimal risk projects of a highly specified nature are Exempt from IRB review. This list of Exempt Category projects is defined by federal regulations (45 CFR 46 101.b). OPHS staff conduct an initial review of proposed activities to ensure the activities qualify for exemption under those regulations.

It should be noted that “Exempt” does not simply mean exempt from any review. Again, all research involving human subjects must be reviewed by OPHS staff, and where appropriate referred to the IRB Chair and/or Full Board.

If the project meets these regulatory definitions, the proposed project is deemed “Exempt” from further review, with the IRB Chairperson and/or Director signing off on that determination. The project is then listed on the OPHS monthly “Chair’s Report” as an Exempt category project and filed accordingly.

In most cases, no further action is ever taken with Exempt category projects. However, if the investigator plans to revise such a protocol, they are required to notify OPHS in advance, who will again determine if the project still meets federal Exempt category definitions and regulations.

To facilitate the review process for such projects, OPHS has developed an Exempt Category Review form for completion by the Principal Investigator (see Appendix C-IRB Forms and Instructions).

Note that if, in the opinion of OPHS staff and/or the IRB Chair, the proposed project does not meet regulations for Exempt Category review, it is then re-assigned to a higher level of Review (Expedited or Full Board).

5.4 New Submissions (Non- Exempt Protocols)

All UNTHSC investigators proposing to initiate a research activity involving human subjects, that does *not* qualify as exempt from IRB review, must submit a new study application to the IRB after which OPHS staff review for completeness, and if appropriate assign the protocol for review to determine whether the involvement of human beings protects their right and welfare based on the criteria for IRB approval listed at 45 CFR 46.111 and 21 CFR 56.111. OPHS staff are available to assist investigators in determining which IRB application to complete for non-exempt protocol submissions.

Expedited/Full Board Review

New submissions may be processed by expedited review (often one or two IRB members conducting a review) or may require review at a convened meeting of the UNTHSC IRB (reviewed by the committee).

The determination of the type of review is made by OPHS staff and is based on the provisions of federal regulations. The investigator is required to submit a completed and signed IRB Application (Expedited or Full Board as appropriate), a protocol synopsis with description of the research methodology and procedures, all informed consent documents, recruitment ads, flyers, questionnaires, federal grant application (if applicable), clinical protocol and investigator's brochure (if applicable), correspondence related to this protocol from the sponsor, curriculum vitae of the Principal Investigator, conflict of interest (COI) statements for each listed project personnel, and certificates of training in human subjects research for each project personnel not currently on file with OPHS. See Section 5.13 and 5.14 for more details about preparing Expedited and Full Board IRB applications for submission

Typically, an Expedited Review can be completed with 1-2 weeks, unless critical information is absent, which then adds to review time.

Full Board reviews are scheduled monthly with the schedule published and available on-line (for current review schedule, see website link at <http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Review%20Schedule#FY2009-10>)

Facilitated Review

The UNTHSC IRB may rely on reviews completed by other duly-constituted IRBs (as arranged under IRB Authorization Agreements). Such arrangements will designate those IRBs under the UNTHSC Federalwide Assurance (FWA). New protocols that have been reviewed and approved by these designated IRBs undergo a “facilitated review” at UNTHSC. In this review process, a designated and experienced IRB member makes a determination as to whether the review conducted by the other authorized IRB meets the requirements of UNTHSC for the inclusion of human subjects in research.

UNTHSC investigators are required to submit an IRB Application, all appropriate and relevant materials, consent forms, and documents for review. In addition, a copy of the other IRB's approval letter and all materials reviewed by that IRB must be submitted for UNTHSC facilitated review. In this manner, Facilitated Review at UNTHSC serves to ensure that:

- The proposed protocol adheres to UNTHSC requirements for ensuring the protection of human subjects;
- UNTHSC has adequate facilities and staffing to carry out the proposed research;

- The proposed consent form includes language that addresses UNTHSC's institutional policies and requirements;
- An appropriate consent and assent (where applicable) process will be followed;
- An appropriate authorization for the use of protected health information (PHI) in a research setting is issued.

As part of a special arrangement, such facilitated reviews may be conducted for projects involving UNTHSC students engaged in Clinical Research Management (CRM) program internships at non-UNTHSC sites. In this situation, a letter from the CRM Program director shall serve as the IRB application. As stated above, all other documents shall be provided by the CRM Program Director for each student internship project at these sites; the internship activity will be reviewed and entered in the record under the appropriate review category.

5.5 Applications Lacking Definite Plans for Involvement of Human Subjects Submissions

The Director of the OPHS, and designated OPHS staff members are designated and authorized by these principles and procedures to perform the initial review of studies falling in the following categories:

1. Applications for approval of Center, Training or Program Project Grants, where the application outlines the administrative core requirements and does not include a plan for the involvement of human subjects.
2. Review of data coordinating centers, or similar entities that involve access to private and identifiable information about living individuals, requires review by a member of the OPHS and/or IRB.
3. Applications requesting approval for development purposes only under 45 CFR 46.118, where the proposals lack definite plans for the inclusion of human subjects.

The Principal Investigator (PI) is required to submit a grant/contract application to OPHS who will review the application and send correspondence acknowledging the submission of the grant and that the project does not have definite plans to involve human subjects. The PI must resubmit a new study application prior to conducting any research with human subjects.

5.5 Continuing Review Submissions

In accordance with federal regulations, the UNTHSC IRB requires that all ongoing research protocols undergo continuing review at intervals appropriate to the degree of risk, but not less

than once per year (defined as 365 days: see 45 CFR 46.109(e) and 21 CFR 56.109(f)). The frequency and extent of continuing review for each study is based upon the nature of the study, the degree of risk involved, the novelty of the research procedures, and the vulnerability of the study subject population. After a careful consideration of each of these factors, each protocol is assigned an approval period, after which it must be re-reviewed by the IRB.

In some instances, such as the use of innovative research techniques, the IRB may choose to grant an approval period based on a small number of subjects accrued rather than on a specific time period. This type of approval is usually assigned when there are concerns regarding the potential risks of participation.

Each investigator must abide by the approval period imposed by the IRB at the time of the most recent IRB approval. Each IRB approval notice designates a period of time during which activities involving human research subjects may be undertaken. No investigator may continue to recruit, enroll, or treat subjects or analyze data after the IRB approval expiration date. Continuation of the research after the date of expiration of IRB approval is a violation of federal regulations (see 45 CFR 46.103(b)(4) and 21 CFR 56.103(a)).

To assist investigators in fulfilling the requirement for continuing review, OPHS sends Principal Investigators written documentation specifying the approval period and expiration date at the time of initial approval. This is the “first notice.” As the expiration date of the protocol approaches, a “Request for Continuing Review/Progress Report” letter and a Progress Report Form will be sent via campus mail to the principal investigator or his/her designee. The letter will include a due date for when materials should be submitted to OPHS. A final notice of continuing review will be sent to investigators via email if materials are not received by the due date. If investigators do not forward a completed application for continuing review before the protocol expiration date, and in sufficient time for distribution and review by the IRB, OPHS and the IRB cannot guarantee that the application will be reviewed before the date of expiration.

It is the investigator’s responsibility to ensure that approval period for an active protocol remains current. The IRB expiration date can be found on the IRB Board Action and Notice of Approval letter for projects that have not been reviewed for continuation. For projects that have undergone continuing review previously, the expiration date can be found in the IRB Board Action that was sent at the time of the most recent continuing review. Investigators must submit a continuing review (i.e. Progress Report) to OPHS which includes the status (e.g. open to enrollment, closed to enrollment, data analysis only, etc.), number of subjects enrolled, summary of adverse events and the study results.

Depending on the status of the study, two types of continuing review submissions can be submitted:

Final Reports

There are several types of final reports, including:

- Completed/Closed: If the study is completed and no more data analysis is to be done, indicate the study status as “Completed/Closed.” In this case, the study will be marked as “Completed” by OPHS and the IRB.
- Enrollment, research intervention, subject follow-up complete, data analysis only continues: If all subject enrollment, research intervention, and subject follow up is complete, and only data analysis continues, it is appropriate to close out the study. In this case, the study will be marked as “Completed” by OPHS and the IRB.
- Project terminated before completion: List the date and the reason that the project is terminated. In this case, the study will be marked as “Terminated” by OPHS and the IRB.
- Project has not been and will not be conducted: List the reason the project will not be pursued. In this case, the study will be marked as “Withdrawn” by OPHS and the IRB.

Continuing Review (Ongoing)

If any study activities will continue past the current expiration date of the study, a continuing review application is required. This would include projects that are:

- Actively enrolling new subjects;
- Enrollment complete, but research intervention continues;
- Enrollment and research intervention complete, subject follow up continues;
- Projects not yet started;
- Projects on hold.

Additionally, depending upon the situation, some projects may be reviewed for continuation and left open when enrollment, research intervention, subject follow-up complete, data analysis only continues.

As always, if the IRB has not reviewed and approved the continuing review of the study by the study’s current expiration date, research activities must stop and no new subjects may be enrolled in the study.

Objective of Continuing Review

The IRB performs continuing review in order to systematically monitor previously approved research to document that the requirements imposed by the IRB during the initial review of the protocol continue to sufficiently protect subject safety and welfare.

A second objective of continuing review is to confirm that all information presented to subjects is complete, accurate, and up-to-date. The investigator must submit a continuing review application to OPHS which includes:

- A completed Progress Report (see Appendix C) that contains relevant information required to determine whether the proposed research continues to meet the regulatory criteria for approval. This includes the number of human subjects accrued, a description of any adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
- A summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;
- Copies of the current protocol synopsis for the study (with the IRB stamp);
- Copies of the current informed consent document for the study (version with IRB stamp and a "clean" version without the IRB stamp);
- Any relevant data safety committee or multi-center trial reports (Data Safety Monitoring Board, audits, Contract Research Organization (CRO), etc...);
- Other items as needed, such as questionnaires, recruitment ads, etc.

Please Note: A description of how to compile continuing review applications for submission to OPHS appears later in this section.

As in their initial review, members evaluate the study purpose, procedures, risks, potential benefits, alternatives, subject selection, informed consent, protection of the privacy of subjects and the confidentiality of their data, safety monitoring procedures, and additional protections for vulnerable populations as set forth in 45 CFR 46.111 and 21 CFR 56.111.

Finally, the Board may request an Audit if projects need verification from sources other than the investigators to determine that no material changes have occurred since previous IRB review. It is the role of the IRB to determine which projects need verification from sources other than the PI regarding changes since the last IRB review. The criteria used by the IRB to make these determinations could include some or all of the following:

- Randomly selected projects;
- Complex projects involving unusual levels or types of risk to subjects;

- Projects conducted by investigators who previously have failed to comply with the requirements of Health and Human Services regulations or the requirements or determinations of the IRB; and
- Projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.

Levels of Continuing Review Submissions

Continuation submissions may receive full committee or expedited review according to the status of the research.

Full Committee Review

Studies that do not meet the criteria for expedited review, and fall into one of the following categories must undergo full committee review:

1. Actively enrolling new subjects and/or providing research-related interventions to previously enrolled subjects.
2. Subject accrual is complete and previously enrolled subjects continue to receive research-related interventions.

Expedited Review

Studies whose status falls into one of the following categories qualify for expedited review:

1. Research permanently closed to the enrollment of new subjects. All subjects have completed all research-related interventions and the research remains active only for the long-term follow-up of subjects.
2. Research previously approved by the fully-convened IRB where no subjects have been enrolled and no additional risks have been identified.
3. Research in which the remaining activities are limited to data analysis only.
4. Research previously reviewed by the IRB via expedited review procedures.

Facilitated Review

Continuations of protocols previously reviewed and approved by another, duly authorized and designated IRB (see above) will be reviewed by Facilitated Review. The objectives of facilitated *continuing* review mirror those for continuing reviews completed by the UNTHSC IRB.

The facilitated reviewer is responsible for ensuring that the study continues to meet the requirements for the protection of human subjects. Because the other IRB must provide all modifications and adverse event reports to the UNTHSC IRB as well, the facilitated reviewer has access to a summary of all modifications and safety or other reports.

Upon approval, the consent (and assent where appropriate), recruiting documents, and a HIPAA authorization form (if any) are re-issued and re-stamped as needed for protocol purposes.

Submitting Continuing Review or Final Report Applications to OPHS

This section describes how applications for continuing review and final report/close outs should be compiled (i.e. put together) before they are submitted to OPHS. Please note that failure to compile the application appropriately may result in a delay in review and/or return of the application to the investigator.

Full Board Protocols

For Full Board protocols, the continuing review application should be submitted to OPHS by the requested deadline (usually the 3rd Monday of each month) in the following manner:

1. One copy of the completed and signed Progress Report Form;
2. One copy of a NEW (updated) Conflict of Interest form for each of the key personnel listed on the protocol;
3. 20 **compiled** packets, each containing the protocol synopsis (current IRB-approved stamped version), each consent form (current IRB approved stamped version), and an executive summary of any data safety committee or multi-center trial reports (if applicable/available);
4. One copy of each consent form (current IRB approved version without the IRB stamp);
5. One copy of the complete data safety committee or multi-center report (if applicable);
6. One copy of a summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;
7. One copy of other items (as needed) such as questionnaires, recruitment ads, etc.

Expedited Protocols

For Expedited protocols, the continuing review application should be submitted by the requested deadline to OPHS in the following manner:

1. Two copies of the completed and signed Progress Report Form;
2. One copy of a New (updated) Conflict of Interest form for each of the key personnel listed on the protocol;
3. 2 compiled packets, containing the protocol synopsis (current IRB-approved stamped version) and each consent form (current IRB approved stamped version);
4. One copy of each consent form (current IRB approved version without the IRB stamp);
5. One copy of a summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;
6. One copy of other items (as needed) such as questionnaires, recruitment ads, etc.

Final Reports/Close Outs

Final reports do not require new (updated) Conflict of Interest forms for each key personnel listed on the study. Final reports should be compiled in the following manner:

1. One copy of the completed and signed Progress Report Form closing out or terminating the study;
2. One copy of each consent form (current IRB approved stamped version);
3. One copy of a summary of any recent literature, findings, or other relevant information.

Full Board Protocols-Continuing Review with Study Amendment

1. One copy of the completed and signed Progress Report Form;
2. One copy of a NEW (updated) Conflict of Interest form for each of the key personnel listed on the protocol;
3. 20 **compiled** packets, each containing a cover memo describing the request for modification to the study, the "tracked changes" version of the current IRB-approved protocol synopsis, "tracked changes" versions of each IRB approved consent form, "tracked changes" versions of any revised questionnaires, recruitment ads, etc and/or any new questionnaires, recruitment ads, etc. Also include an executive summary of any data safety committee or multi-center trial reports (if applicable/available);
4. One "clean" copy (with changes accepted) of the revised protocol synopsis, revised consent forms, and revised questionnaires, recruitment ads, etc;

5. One copy of any new questionnaires, recruitment ads, etc;
6. One copy of the complete data safety committee or multi-center report (as applicable);
7. One copy of a summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;

Expedited Protocols-Continuing Review with Study Amendment

1. Two copies of the completed and signed Progress Report Form;
2. One copy of a NEW (updated) Conflict of Interest form for each of the key personnel listed on the protocol;
3. 2 **compiled** packets, each containing a cover memo describing the request for modification to the study, the "tracked changes" version of the current IRB-approved protocol synopsis, "tracked changes" versions of each IRB approved consent form, "tracked changes" versions of revised questionnaires, recruitment ads, etc., and/or any new questionnaires, recruitment ads, etc;
4. One "clean" copy (with changes accepted) of the revised protocol synopsis, revised consent forms, and revised questionnaires, recruitment ads, etc;
5. One copy of any new questionnaires, recruitment ads, etc;
6. One copy of a summary of any recent literature, findings, or other relevant information, especially new information about risks associated with the research that may affect the subjects' willingness to continue participation;

5.6 Expired Protocols

Protecting Enrolled Subjects

If continuing approval is not issued prior to a study's expiration date, the study will be **inactivated**. The OPHS will forward a study expiration notice to the PI requiring all human research activity (including data analysis) to stop.

In the event that a protocol expires and the withdrawal of research interventions may place subjects of the study at risk, the investigator may request that the IRB grant permission to allow the continuation of activities required for subject safety prior to renewal of IRB approval. To make such a request, the investigator must forward the following items to the IRB:

1. Completed continuing review application that includes all applicable attachments;

2. An explanation of why the submission of the continuing review application was delayed;
3. A discussion of why the suspension of research activities would adversely impact subject safety or go against the subject's best clinical interest; and
4. If research-related interventions have been continued with a subjects on an expired protocol, a discussion of the circumstances that necessitated this action.

Each request will be forwarded to the IRB Chair for consideration. If the IRB Chair grants permission to allow the continuation of research interventions with previously enrolled subjects for reasons related to subject safety, the IRB will send written notification to the investigator. Other research activities (such as recruitment, enrollment, data analysis, etc.) may only be resumed after the investigator receives continuing approval for the research.

Research where the principal investigator fails to respond or provide adequate documentation for a continuing review within 3 months (90 days or more) after IRB approval will be administratively closed by OPHS.

Additionally, research where the principal investigator has left the institution and did not notify the IRB (or amend the protocol by replacing themselves with a new principal investigator) within 3 months (90 days) after his/her departure will be administratively closed by OPHS.

Reactivation of Lapsed Protocols

As noted previously, it is the PI's responsibility to ensure that a request for continuing approval is submitted and approved before the study's upcoming IRB expiration date. It is noted, however, that in some cases it is not possible to prevent a lapse in IRB approval. A new study application must be completed and submitted for IRB review and approval to continue the study. The investigator should include the reason for the lapse along with the NEW protocol review application. The protocol will be forwarded for expedited, full, or facilitated review based on regulatory requirements for the study.

5.7 Amendment Submissions

As discussed above, the IRB is responsible for reviewing and approving any research activity involving human subjects. The parameters under which a human subject may be included in research are outlined by the IRB during the yearly review of a research protocol. Should it become necessary to modify any aspect of the previously approved protocol, or implement requirements previously imposed by the IRB, an investigator must file and receive approval for an amendment to the previously issued IRB approval.

Proposed changes may not be implemented until the IRB has reviewed and approved the modifications to the previously approved protocol, except when the changes are necessary to eliminate apparent, immediate hazards to subjects. If such immediate changes are felt to be

necessary, the investigator must notify the IRB within 72 hours as to the nature of the changes and why immediate action was required.

All UNTHSC investigators proposing modifications to a previously approved human subject research project must submit a signed memorandum detailing the new changes and amendment(s) to the protocol. The “cover letter” must list/detail all proposed changes to the IRB approved study. IRB review of amendment submissions focuses on the effect of the proposed changes on human subjects. The IRB analyzes whether the amendment poses additional risks to subjects or represents a significant change in study procedures.

Levels of Review for Amendments

Amendment submissions may receive full committee, expedited, or administrative review, according to the nature of the proposed changes and their effect on the potential risk/benefit ratio.

Full Committee Review of Amendments

If the changes proposed to the protocol are substantial or if the changes alter the potential risk/benefit ratio of the study, the amendment must be reviewed by the full IRB. Examples of such changes are an increase in dosage of an investigational drug, a significant increase in the total number of subjects (greater than 10%), addition of procedures that increase risk to subjects (e.g. addition of a Positron Emission Tomography (PET) scan), addition of a new subject population (e.g. broadening the eligibility criteria to include children), or significant changes in study design.

Full Board amendments should be submitted to OPHS in the following manner by the deadline date (usually the 3rd Monday of each month):

1. 20 **compiled** packets, each containing a cover memo describing the request for modification to the study, the “tracked changes” version of the IRB current IRB-approved protocol synopsis, “tracked changes” versions of each IRB approved consent form, “tracked changes” versions of revised questionnaires, recruitment ads, etc and/or any new questionnaires, recruitment ads, etc, and an executive summary of any data safety committee or multi-center trial reports (if applicable/available);
2. One “clean” copy (with changes accepted) of the revised protocol synopsis, revised consent forms, and revised questionnaires, recruitment ads, etc. Please Note: The “clean” copies should be paper clipped rather than stapled;
3. One copy of any NEW questionnaires, recruitment ads, etc for stamping. Please Note: These items should be paper clipped rather than stapled.

See Section 5.5 for information on how to submit a full board amendment with a continuing review submission.

Expedited Review of Amendments

If the proposed changes to the protocol are minor, the amendment may qualify for expedited review. The IRB defines “minor modifications” as any change in the previously approved protocol that does not deviate significantly from the requirements for approval during the previous IRB review. Examples include editorial changes to the protocol or consent form, the addition or deletion of an investigator, a minor change in sample size (less than or equal to 10%) and/or the addition of a procedure that does not pose more than minimal risk to study participants (e.g., the addition of a small volume blood draw).

The IRB Chair or Vice Chair may conduct a review and approve amendments that are limited to the following categories:

- Review and approval of changes in protocol and/or personnel that do not result in increased risk to subjects. For example, changes in the study coordinator or the addition of investigators having similar education and background, or minimal changes in procedure that do not impact the overall risk profile of the protocol;
- Review minor modifications to the Informed Consent Form, recruitment advertisements, and other study documents, (e.g., changes in address, changes in telephone number, or change in contact person);
- Review and acceptance of contingencies noted by the IRB during a previous review of a study. For example, the receipt of IRB approval documentation from a non-UNTHSC site, the receipt of a federally-issued certificate of confidentiality, etc.

Expedited amendments should be submitted to OPHS in the following manner by the deadline date:

1. 2 **compiled** packets, each containing a cover memo describing the request for modification to the study, the “tracked changes” version of the IRB current IRB-approved protocol synopsis, “tracked changes” versions of each IRB approved consent form, “tracked changes” versions of revised questionnaires, recruitment ads, etc and/or any new questionnaires, recruitment ads, etc;
2. One “clean” copy (with changes accepted) of the revised protocol synopsis, revised consent forms, and revised questionnaires, recruitment ads, etc. Please Note: The “clean” copies should be paper clipped rather than stapled;
3. One copy of any new questionnaires, recruitment ads, etc for stamping. Please Note: These items should be paper clipped rather than stapled.

See Section 5.5 for information on how to submit an expedited amendment with a continuing review submission.

5.8 Submission of Serious Adverse Event Reports

UNTHSC investigators are required to submit reports of all serious adverse events experienced by human subjects by completing IRB Form 3a or 3b and submitting it to OPHS. Refer to Chapter 7.4 for adverse event reporting requirements and more information.

PIs of protocols reviewed and approved by outside (non-UNTHSC) IRBs are responsible for reporting any on-site serious adverse events, by completing IRB Form 3a and submitting it to OPHS.

5.9 Submission of Relevant New Information

Any information relevant to the participation of human subjects in a proposed or approved research project in which UNTHSC is engaged should be submitted to the IRB via OPHS. Examples of relevant materials include documentation of temporary study suspension by the sponsor, clarification of subject complaints, audit reports, or notice of Food and Drug Administration approval of study drugs or devices.

In some cases, these materials may require consideration by a convened IRB. In each instance, the IRB will determine whether the new information should be relayed to enrolled subjects.

5.10 Submission of Investigator Responses to IRB Correspondence

During the IRB review process, all requests for modifications or further clarifications from the IRB are documented in a letter and sent to the investigator by OPHS staff via email and hard-copy mail (campus mail or USPS). The investigator's response to the IRB correspondence is evaluated in accordance with the requirement set forth during the initial review (i.e., returned to the full board, forwarded to a designated IRB member reviewer, or forwarded to the OPHS staff member for follow-up by the IRB Chair). The correspondence between the IRB and investigator/researchers are recorded and stored by OPHS. Responses that are appropriate for evaluation by the IRB Chair (or an IRB member designee) include the following:

- Response limited to the finalization of formatting/wording of consents, assents, recruitment, or other study documents where the requested change does not significantly alter the draft last reviewed by the IRB;
- Evaluation of contingencies or other administrative requirements that do not impact the potential risk/benefit ratio of the submission.

5.11 Levels of IRB Review

This section gives an overview of the three levels of review found in the “Common Rule” (45 CFR 46) and review procedures for each. The levels of IRB review are applied to initial review of the project or activity, revisions or amendments, and continuing review. The levels are:

1. Exempt review (protocols involving minimal risk and falling within one of six defined categories as described and defined below in section 5.12); and
2. Expedited review (protocols involving no more than minimal risk and falling within one of nine defined categories as described and defined in section 5.13 below); and
3. Full board review (protocols involving greater than minimal risk)

Certain studies may have the characteristics of human subject research but may not meet the regulatory definition. At UNTHSC, these studies are considered Not Human Subjects Research (NHSR) because they do not meet the federal definitions of human subjects and/or research. Any investigator who is unsure of whether their proposal constitutes “human subject research” should contact OPHS for guidance. OPHS staff will determine if the study is human subject research based on the methodology, the subjects involved, whether identifiers will be collected and stored, how the information will be used, and risks to the subjects. UNTHSC policy does not allow investigators to make this determination themselves. If a study does not qualify as human subject research, OPHS will issue a letter stating the project does not require IRB review or approval.

5.12 Exempt Human Subjects Research

Section updated (page 64) on 8/10/10 (clarification on Exempt category reporting).

The UNTHSC OPHS will review all human subject research activities under their jurisdiction to determine whether research meets one or more of the exemption categories described in the federal regulations. OPHS will assist the IRB to ensure that proposed research activities comply with UNTHSC’s ethical standards.

Research may be granted exempt by the OPHS if all research activities involve procedures listed in one or more of the specific categories under 45 CFR 46.101(b). FDA regulated research does not qualify for exempt status other than exempt category 6, food and taste evaluations. FDA regulations allow for one emergency use of a test article in an institution without prospective IRB review, provided that such emergency use is reported to the IRB within five (5) working days after such use. For more information on the emergency exemption from prospective IRB review, see Chapter 15.3 on “Emergency Use of an Investigational Drug, Biologic, or Device.”

Only OPHS staff, the IRB Chair, Vice Chair, or IRB designee may determine which research activities qualify for an exempt review. Investigators do not have the authority to make the independent determination that their research involving human subjects is exempt.

Exempt research activities require the same subject protections and ethical standards as those outlined in The Belmont Report. Research conducted under exempt review is subject to all applicable UNTHSC Institutional policies, IRB and OPHS principles and procedures, appropriate state laws and possibly the Health Insurance Portability and Accountability Act

(HIPAA) regulations. The investigator is responsible for assuring that the exempt research is carried out in an ethical manner that includes appropriate subject protections.

OPHS and the IRB shall determine those projects which need verification from sources other than the investigators to ensure that no material changes have occurred since previous IRB review. The criteria used by the IRB to make these determinations may include some or all of the following:

- Randomly selected projects;
- Complex projects involving unusual levels or types of risk to subjects;
- Projects conducted by investigators who previously have failed to comply with the requirements of the Health and Human Services (HHS) regulations or the requirements or determinations of OPHS and/or the IRB; and
- Projects where concern about possible material changes occurring without OPHS and/or IRB approval have been raised based upon information provided in continuing review reports or from other sources.
- An investigator may request a particular category of exemption, but the final determination will be made by the IRB Chair, Vice Chair, or IRB designee.
- Research cannot be granted exempt status in the following situations:
 1. The research uses deception (research in which the investigator does not disclose the true purpose of the research to subjects, or the results of the subject's participation in the study). Generally, studies using deception must receive expedited or full board review. However, the IRB may determine studies to be exempt when the omission of minor information is part of the study design and the omission presents no possible risk to subjects. These cases are technically different from deception studies. The omission of minor facts is not equivalent to deception.
 2. The subjects are prisoners;
 3. When conducting FDA regulated research (note: only exempt category 6, taste and food quality evaluations, may qualify as exempt).

Exempt Research Categories (§46.101(b)):

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: (i) Research on regular and special education instructional strategies; or (ii) Research on the effectiveness

of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and any disclosure of the human subjects' responses outside of 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. If the research involves children participants, the research must be limited to educational tests (cognitive, diagnostic, aptitude, achievement), and observation of public behavior when the investigator(s) does not participate in the activities being observed. Research involving children that uses survey procedures, interview procedures, or observation of public behavior when the investigator(s) participates in the activities being observed cannot be granted an exemption.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 45 CFR 46.101(b)(2) if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. To qualify for this exemption, data, documents, records, or specimens must have been collected before the research project begins.

Example: Investigator A wishes to screen blood samples at a rural hospital for incidence of HIV infection. They do not want to draw specimens specifically for this purpose; rather they propose to use specimens that were drawn for some other purpose but which remain in the hospital laboratory. If Investigator A proposes to use specimens that had been drawn prior to the initiation of their research and are, for some reason, "on the shelf," the protocol may qualify as exempt, assuming the other requirements are met (i.e., the sources are either publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects). If they propose to use specimens that will be drawn after the start date of their project, for reasons unrelated to their research, the protocol is not exempt, even though the specimens will be drawn regardless of the researcher's use of the excess blood. The protocol may, however, qualify for expedited review. Under this exemption, an investigator (with proper

institutional authorization) may inspect private, identifiable records, but may only record information in a non-identifiable manner. The data must be permanently and completely de-linked at the time of extraction. A code may be used to organize data as it is collected. However, the code may not be a means of re-linking the data set to the original data source.

Example: Investigator B wishes to examine court records of involuntary commitments to psychological institutions. If they use court records that were on file before the initiation of their research, the protocol may qualify as exempt. If they propose to use records filed after the initiation of the project, the protocol is not exempt, although it may qualify for expedited review.

Case Reports: OPHS and the IRB acknowledges that it is common professional practice to develop and publish case reports as a means of sharing insight and knowledge gained from the evaluation and treatment of unique clinical situations. Because case reports do not usually contain private and identifiable information about a living individual and generally do not meet the regulatory definition of "research," the UNTHSC IRB does not require review of these activities. Investigators should be aware that journals are requiring proof of exemption or IRB approval before a case report is accepted for publication. For this reason, the OPHS and the IRB encourages investigators to proactively seek IRB approval and exemption for case reports. Exemption from IRB review is generally granted under Category #4 for case reports.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii) Procedures for obtaining benefits or services under those programs; (iii) Possible changes in, or alternatives to, those programs or procedures; or (iv) Possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies 21 CFR 56.104(d). If wholesome foods without additives are consumed, or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe or agricultural chemical or environmental contaminant at or below the level found to be safe by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture

Procedures for Submission and Review of Exempt Research

Investigator Responsibilities

The investigator submits a completed and signed Request for Exempt Review form with appropriate attachments. The Principal Investigator (PI) indicates the criteria under which the exemption is believed to be appropriate (45 CFR 46.101(b)) and replies to all requests for revisions and/or clarifications requested by OPHS.

OPHS Responsibilities

The OPHS staff conduct a review of the project to determine if it qualifies for exempt status according to UNTHSC OPHS and IRB policy and human subjects research regulations. The staff determine if the research meets the ethical standards of the Belmont Report by consulting the criteria for approval. The staff may request minor revisions in order to facilitate review, and notify the investigator when the study does not meet criteria for exempt status. The OPHS staff determine the appropriate level of review, communicate this to the investigator, and guide the investigator with required resubmission at the required level. If needed, the Chair, Vice Chair, or designee is available to assist OPHS staff with exempt determinations. Exempt studies may be approved by OPHS staff, the IRB Chair, Vice Chair, or designee.

Approval letters are generated by OPHS staff. Exempt determinations are distributed to IRB members through meeting minutes, Chair's Reports, or other documentation as appropriate at a future meeting of the convened IRB.

Amendments and Revisions to Exempt Research

If the investigator makes changes to a study that was previously determined to be exempt by the OPHS and/or IRB, the investigator is required to submit the proposed revisions to OPHS as an amendment to the protocol. Such changes may not be implemented prior to OPHS review and/or IRB approval, per federal regulations. Certain changes may disqualify the research from exempt status; therefore, all changes in the research plan must be reported to the OPHS for review and approval, prior to implementation.

Amendments to EXEMPT category research should be submitted to OPHS in the following manner:

1. Cover memo describing the request for modification to the study;
2. Revised IRB Application (if appropriate);
3. One "Tracked Changes" copy of any revised documents, such as descriptions of research procedures, research statements, surveys, questionnaires, etc.
4. One "clean" copy (with changes accepted) of the revised documents. Please Note: The "clean" copies should be paper clipped rather than stapled;

5. One copy of any new questionnaires, recruitment ads, etc. Please Note: These items should be paper clipped rather than stapled.

5.13 Expedited Review

According to the federal regulations: “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.” Risk includes not only physical risk, but also psychological, emotional, legal, social, and financial risks. The definition of minimal risk serves as the starting point for the determination of the category of review.

If a project meets the definition of minimal risk, and falls into an expedited category, as described below, the Chair, Vice Chair, or designee may review and approve the project.

Expedited Reviewers

Expedited review may be carried out by the IRB Chair, Vice Chair or by an experienced IRB member designated by the IRB Chair or Vice Chair for their expertise in a given research area. To qualify as an expedited reviewer, the IRB member, according to the judgment of the IRB Chair or Vice Chair, must have the experience and education required to conduct expedited review.

The designated reviewer(s) may exercise all of the authorities of the IRB, except for disapproving the research (a research activity may be disapproved only after review by the full committee). If the reviewer and investigator cannot agree on the changes required to secure approval, the application will be sent to the convened IRB for Full Board review. The reviewer may refer the application to the full board for review at any time.

Although expedited review requires fewer steps than full committee review, it is not a lesser review process – all of the requirements for the protection of human subjects are applied equally in expedited review and the same standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review categories of research.

If a research study is found to be ineligible for expedited review, it will be added to the next possible full committee meeting agenda for review.

Expedited protocols are required to go through yearly continuing review.

An investigator may request a particular category of expedited review, but the final determination of applicability will be made by the OPHS and the IRB Chair. Research may be granted expedited status by the IRB if all research activities involve procedures listed in one or more of the specific categories under 45 CFR 46.110.

General Restrictions on Expedited Review

We at UNTHSC concur with current federal regulatory guidance, which states that expedited review procedures are not appropriate for research involving prisoners at UNTHSC.

Expedited review procedures may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. Additionally, the expedited review process may not be used in the review of classified research.

Expedited Review Categories

Federal regulations 45 CFR 46.110, 21 CFR 56.110 and 38 CFR 16.110 allow for IRB review of nine specific categories of no more than minimal risk research through expedited review procedures under the conditions listed below. The IRB may use an expedited procedure to conduct initial review of research provided that research activities do not fall under any of the general restrictions, present no more than minimal risk to human subjects, and involve procedures listed in one or more of the following categories 45 CFR 46.110(F)/21 CFR 56.110(F):

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 increase the risks, or decrease 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, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight-week period and collection may not occur more frequently than two times per week; or (b) From other adults and children, when 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 are considered. For these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period and collection may not occur more frequently than two times per week. Children are defined in the federal regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" see 45 CFR 46.402(a).

3. Prospective collection of biological specimens for research purposes by noninvasive means. For example: (a) Hair and nail clippings in a non-disfiguring 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 before or during labor (h) Supra and sub gingival 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 scrapping or swab, skin swab, or mouth washings; and/or (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 of procedures that can be expedited include: (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 non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may meet exemption under 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 meet exemption under 45 CFR 46.101(b) (2); this listing refers only to research that is not exempt.

8. Continuing review of research previously approved by a full IRB as follows 45 CFR 46.110(F)(8)/21 CFR 56.110(F)(8): (i.) Where 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 (ii.) Where no subjects have ever been enrolled (at any site, if multi-center trial) and no additional risks have been identified; or (iii.) Where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened full IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified 45 CFR 46.110(F) (9)/21 CFR 56.110(F) (9).

Criteria for Expedited Approval

In order to approve research, the reviewer is required to determine that all of the following requirements are satisfied 45 CFR 46.111:

1. Risks to subjects are minimized: (a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (b) 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 will 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 will 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 must take into account the purpose(s) of the research and the setting in which the research will be conducted and must 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 CFR § 46.116;

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by CFR § 46.117 and state laws;
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, the IRB will ensure additional safeguards have been included in the study to protect the rights and welfare of these subjects. Expedited review may be completed for minimal risk research that adheres to the requirements of 45 CFR 46 subparts B, C, or D.

Procedures for Expedited Review

OPHS staff initially evaluates all submissions recommended for processing by expedited review procedures. OPHS staff prepares a staff review that is forwarded to the IRB Chair or Vice Chair for review and approval. In the staff review, the reasons why the submission meets expedited review criteria is noted by citing the appropriate expedited review category or summarizing the nature of the modification.

The expedited reviewer is prompted to either concur or disagree with the staff's recommendation for expedited processing, and any related contingencies or necessary revisions. The expedited reviewer has access to all necessary application materials for effective protocol review. Expedited research applications should be submitted to OPHS in the following manner:

1. 2 compiled packets containing the Expedited Review Application (original PI signature on one copy), protocol synopsis, and informed consent. If applicable, also include recruitment materials, surveys/questionnaires, telephone scripts/oral scripts, assent forms/parental permission forms;
2. Letters of permission/cooperation, and/or approvals from other IRBs/research sites;
3. One copy of relevant grant applications (if applicable) ;
4. One copy of the Investigator's brochure (if one exists);
5. Conflict of Interest disclosure forms for each person listed as study personnel;
6. Human subject research training certificates for those persons not already on file with OPHS.

The expedited reviewer is responsible for evaluating the project to ensure that the rights and welfare of human subjects are protected and that all criteria for IRB approval have been addressed. The expedited reviewer is also responsible for determining whether the study can be approved with or without changes and whether clarifications are required.

The expedited reviewer forwards any requests for clarification to the assigned OPHS staff member, who will forward such correspondence to the investigator. The investigator's response to correspondence arising from expedited review procedures need only be evaluated by the expedited reviewer. An expedited reviewer may not disapprove a project. In the event that the expedited reviewer makes a recommendation that is not accepted by the investigator, the designated reviewer has two options: 1) Accept the investigator's justification for not incorporating the recommendation and proceed with the approval of the study; or 2) Reject the justification and forward the submission to the next fully convened IRB meeting for further consideration of the issue.

A research activity may be disapproved only after review by the fully convened IRB. The reviewer may request review of the research by an expert consultant for issues which require expertise beyond or in addition to that available on the IRB committee. Documentation that the consultant does not have a conflict of interest is also conducted by OPHS staff.

Standard requirements for informed consent or its waiver or alteration apply to all studies meeting criteria for approval under the expedited criteria. (See Section 9.7 for the IRB Policy on Waiver of Informed Consent.)

If a study is approved under expedited review, the approval notice will indicate that expedited review procedures were followed and will note the expedited review category under which the approval was granted or will include a description of the nature of the modifications processed under expedited review.

Information obtained during the review of an amendment, adverse event, sponsor notification, or other pertinent information may disqualify a study from being approved under an expedited procedure. In this situation, the study is forwarded to the full IRB for determination.

All IRB members are apprised and acknowledge/affirm (at the next scheduled IRB meeting) research projects reviewed by expedited procedures.

5.14 Full Board Review

All human subjects research projects involving greater than minimal risks are reviewed at a fully-convened IRB meeting.

Meeting Schedule for UNTHSC IRB

The UNTHSC IRB usually meets the first Tuesday of each month, unless there is a holiday conflict with the usual schedule, such as Fourth of July, Labor Day, New Year's Day. In this case, the meeting will be held on the second Tuesday of the month. A calendar for submission

and review dates is available from OPHS and is on the OPHS website at:

<http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Review%20Schedule>

Investigator Responsibilities / Full Board Protocol Study

The investigator submits a complete IRB application with appropriate attachments. The PI replies to all requests for revisions and/or clarifications requested by OPHS and/or the full board, when applicable.

Full Board Review Procedures

The IRB observes the following requirements for each convened meeting:

1. A majority of the members of the IRB and at least one non-scientist and one nonaffiliated member (can be the same member with dual roles) must be present.
2. If the required number of members is lost during a meeting (e.g. a member leaves the meeting early) no action may be taken until the quorum is restored.
3. In order for a research project to be approved, it must receive the approval of a majority of the members present at the meeting.
4. Of those voting, no IRB member may be the PI, co-investigator, or have otherwise significantly contributed to the design and conduct of the proposed research study, or meet the criteria for a financial conflict of interest in a protocol being reviewed as defined in this manual; or have other interests or relation to the protocol or the investigator that may affect their objectivity.
5. Assessment of potential conflict of interests are initially identified and communicated by OPHS staff to the IRB Chair. At the start of each IRB meeting, the IRB Chair is responsible for reminding members of the requirement to disclose conflicting interests. The Chair will then poll members present for any conflicting interests not previously declared or identified by OPHS staff.
6. A member with a potential conflicting interest in a protocol may be invited to provide background information regarding the research project as well as answer questions from the Board. However, they will be asked to leave the meeting prior to final discussion and before any motion and vote are taken. The meeting minutes will note and record the name of any member who does not participate in the discussion and final vote of a protocol because of a conflicting interest with the protocol under consideration.
7. A meeting may be conducted by telephone conference call provided that each participating IRB member has received all pertinent material prior to the

meeting and can actively and equally participate in the discussion of all protocols. Meeting minutes must clearly document that these two conditions have been satisfied and should specify which members were present via conference call.

8. IRB meeting deliberations may be tape recorded to assist with the drafting of meeting minutes and correspondence. Audiotapes of IRB meetings may be maintained until the final version of the minutes is approved by the IRB, at which time the tapes will be erased or recorded over.
9. IRB meetings should be scheduled at intervals appropriate to the amount of research requiring review and with sufficient frequency to ensure that the IRB can adequately oversee the progress of the research it has previously approved.
10. Each protocol undergoing initial or continuing review will be discussed and voted upon separately.

Distribution of Meeting Materials

The OPHS office staff distributes all meeting materials either electronically (through email, flash drives, etc.) or via hard copy print documents. It is desirable for IRB members to receive such materials approximately seven to ten (7 – 10) days prior to the meeting date to allow for adequate time to review the materials. Education materials, agenda, and minutes are also provided to IRB members via electronic or hard copy. Meeting materials contain information that is specific to the type of submission. The contents for new, continuation and amendment submissions are outlined below:

New Studies

All members have access to:

- IRB Protocol Application;
- Study Protocol;
- Informed Consent Document(s), if any;
- Assent forms/parental permission forms, if any;
- Recruitment materials, surveys/questionnaires, forms, instruments, telephone scripts/oral scripts, if any;

The grant application and drug and device brochures are also accessible to IRB members.

Continuation Submissions (Annual Reviews, Progress Reports)

All members have access to:

- Progress Reports (Continuing Review, Final report) Form which includes Serious Adverse Event information (if any);
- Currently approved IRB protocol synopsis;
- Last approved or revised Informed Consent Form(s);
- Last approved or revised Assent form(s);
- Data Safety Monitoring Board (DSMB) or auditing reports, including any relevant multi-center trial reports;
- Any other materials included in the submission.

Members have access to any revised documents (recruitment materials, instruments, protocol, etc).

Amendment Submissions

All members have access to:

- Letter or Memorandum describing in detail the nature of the Amendment request;
- Tracked changes versions of the IRB approved revised documents (protocol, consent/assent forms, recruitment documents, questionnaire/surveys, study instruments, etc.) reflecting the changes.
- All previously submitted versions of the protocol, consent/assent forms, complete grant applications, drug/device brochures, modifications, monitoring reports, protocol deviations/exceptions, recruitment documents, and study instruments are also accessible to IRB members.

Serious Adverse Event (SAE) Submissions

A description of all Serious Adverse Events (SAEs) occurring during the designated monthly reporting period (both onsite and offsite) will be prepared by OPHS staff for the monthly Chair's Report. The Chair's Report is distributed to all IRB members prior to the IRB meeting for review. Board members will have the opportunity to discuss any SAEs in which they have concerns or questions with at the IRB meeting. A summary of SAEs for each protocol that occurred during the approval period will also be presented to the Board when protocols are reviewed for continuation or at the time of the final report. Individual SAE reports that are maintained in the protocol file are also accessible to IRB members. See Section 7.4 for more information about SAEs.

Full IRB Review and Determinations

After the IRB Chair has summarized the protocol and any relevant information has been provided by OPHS staff, discussion is opened to all members of the IRB. At this time, other members should note omissions, raise and/or comment upon issues of concern, request clarification on points that are ambiguous, and make suggestions to improve the readability of the consent form and recruitment documents. When all members have had the opportunity to voice their concerns and no further discussion is necessary, the IRB Chair invites the PI or their delegate into the meeting to provide an overview of the study, and address concerns or answer any questions the Board might have. Following such PI interactions, once the Board has no further questions for the PI, the PI leaves the meeting room and any IRM member with a conflict is also asked to leave the room.

At this point the IRB Chair calls for further discussion and a vote on the protocol. The board votes upon the study and makes one of the following determinations:

- If the board determines that the study as written provides adequate protection of human subjects, the board will **approve** the study (with no further changes);
- If the board finds that the application is acceptable, however minor to moderate modifications to the study are necessary to fully address the criteria for approval, the board will **approve the study pending modifications** (to be reviewed and approved by the IRB Chair or Vice Chair);
- If the board has serious concerns about the study, or if significant modifications are required to ensure protection of human subjects, the board will **defer** a vote on the approval of the study until additional information is obtained from the investigator;
- If the board is unable to initiate a discussion of a study due to a lack of time or other circumstances, the board will **defer** (table) the discussion of study for review at a subsequent meeting;
- If the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the risk/benefit ratio is deemed to be unfavorable, the board may **disapprove** the study.

The IRB will approve a study only after determining that the proposed application contains sufficient information to address the criteria for IRB approval cited at (45 CFR 46.111) and (21 CFR 56.111)

An IRB member will make a motion for one of the above options; if seconded by another member of the IRB, the motion is voted upon by the IRB. A majority of the members present at the meeting must vote in favor of the motion for passage.

Discussion and/or deliberations of each study on the meeting agenda shall continue until one of the above motions is passed.

Post-Meeting Correspondence (Board Action)

After each IRB meeting, the appropriate OPHS staff forwards correspondence to investigators whose protocols were reviewed, notifying them of the action/status of their applications. The nature of the correspondence and the process by which an investigator's response is reviewed vary according to the decision made for the study.

- When the board determines that the study as written provides adequate protections, the Board Action indicates the study is approved (with no further changes).
- When the board finds that the application is acceptable, however minor to moderate modifications to the study are necessary to fully address the criteria for approval, the correspondence (attached to the Board Action) indicates the board approved the study pending modifications.
- When a study is approved pending modifications, the OPHS staff composes correspondence describing members' comments and concerns and forwards it to the Principal Investigator after the IRB meeting, as soon as possible. The investigator's response to the correspondence is then reviewed by the Chair/Vice Chair or designee.
- Correspondence indicates when the board previously agreed that a response may be evaluated by a designated reviewer. The investigator's response should be returned to a full board meeting if it fails to adequately address the modifications requested by the IRB. OPHS staff may request additional correspondence identifying outstanding concerns. If, however, the OPHS staff reviewer is of the opinion that the initial response and/or secondary correspondence from the investigator is inadequate, unacceptable, or raises new concerns, the study will be returned to the IRB Chair, Vice Chair or designee, who, if they concur with OPHS staff review, will return the study to the full IRB for further adjudication at the next possible IRB meeting. Correspondence sent to the investigator will indicate these decisions.
- When the board has serious concerns about a study, or if significant modifications are required to ensure protection of human subjects, the correspondence indicates that the board will defer a vote on the approval of the study until additional information is obtained from the investigator.
- When the board is unable to initiate a discussion of a study due to a lack of time or the absence of essential information from the PI, the

correspondence indicates the board will table the discussion of study for review at a subsequent meeting.

- When the application describes research activities that may pose significant concerns for human subject safety with minimal prospect of benefit, or the potential risk/benefit ratio is deemed to be unfavorable, the correspondence indicates the board's decision to disapprove the study. The Investigator will have the opportunity to respond to the board in person or in writing.

In all cases described above a written notification of the IRB's determinations (i.e. approval, conditional approval, disapproval, etc.) will be sent to the investigator. Whenever correspondence is sent, the investigator may call the OPHS staff for clarification of the issues raised. When responding to the IRB's determinations or requests, the investigator may disagree with the board, and provide written justification in support of their viewpoint. The IRB board will then review the investigator's justification and make a determination. It should be noted, however, that the IRB has the final authority to approve or disapprove the research.

Post-meeting correspondence is sent to each investigator via UNTHSC interoffice mail unless OPHS staff is otherwise notified. Investigators may request to pick up correspondence from OPHS if they do not wish to receive such communications via interoffice mail. Additionally, investigators may request for correspondence to be sent to a specific address if they are not located onsite or are not able to receive interoffice mail. It is the responsibility of the investigator or their designee to contact OPHS staff if they feel that they have not received, or are missing, OPHS/IRB correspondence. Failure to do so may result in significant delays to the IRB review/approval process. Investigators can also request that a copy of the correspondence be sent to a designee such as a Co-Investigator, student investigator, research assistance, study coordinator, etc. The "original" correspondence will always be sent to the PI of the study. Investigators are encouraged to contact OPHS staff to discuss their requests and preferences regarding correspondence from the OPHS/IRB. See Appendix F for examples of OPHS correspondence.

Consent Form, Assent Form and HIPAA Authorization Templates

Investigator templates/links for consent forms are available on the OPHS and respective IRB Web pages: <http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Forms>

The consent, assent and HIPAA authorization form templates are generic documents intended to provide guidance in the development of the consent and assent documents for the research project. Investigators should use the suggested headings and text wherever appropriate and should provide protocol-specific information where instructed.

5.15 Appeals Process of IRB Determination

If the investigator believes that the requirements imposed by the IRB are unduly restrictive of the proposed research, they may contest these requirements (in writing) to the IRB. The

investigator's written objection should be submitted to OPHS via email with attached documents in Word.doc or Adobe.pdf format. The objection should contain a cover letter/memorandum outlining the reasons for believing that the proposed research procedures are already in compliance with UNTHSC policy and the applicable federal regulations and should include references from the literature to support the argument. If, after the IRB has deliberated on the investigator's response, the issue has not been resolved satisfactorily, the investigator may appeal the board's decision in writing to the IRB Chair, who may invite the investigator to present their viewpoint at an IRB meeting. If the IRB rejects the appeal, the investigator must comply with the IRB's restrictions or the research will not be approved.

Note that no other entities or officials at UNTHSC may override an IRB decision to disapprove, table or defer a protocol. Other entities or officials may disapprove an approved study. Among the reasons for such disapproval are issues such as inadequate resources, mission objectives of the university or other or university or institutional concerns.

5.16 Length of Protocol Approval

As part of the motion made on a study under review, the IRB makes a decision regarding the length of the approval period. Federal regulations require that every approved study receive continuing review "not less than once per year." Accordingly, an approval period cannot exceed 365 days. In some cases, the IRB may grant a shorter approval period if the complexity or risk level of the study merits more frequent continuing review. As noted previously, in some cases such as the use of innovative research techniques, the IRB may choose to grant an approval period based on a small number of subjects accrued rather than on a specific time period. This type of approval period is usually assigned when there are questions regarding the potential risks of participation. Once this interval has expired, the project must receive continuing IRB review if it is to remain active.

Also, note that amendment approvals do not alter the date of continuing review or the initial approval date of the study.

Each approval letter issued notes a beginning approval date and an ending approval date. The beginning approval date is the day the fully convened board or expedited reviewer granted final approval. The end approval date, however, is not arbitrary. End approval dates can never be more than one year (365 days) from the date of the last IRB review. End approval dates must be calculated carefully, paying attention to IRB meeting dates or dates of expedited review.

As noted in the federal regulations: "An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities..."

Contingencies

Contingencies to approval are conditions or restrictions that are imposed at the time IRB approval is granted. They include requirements that must be fulfilled prior to the enrollment of subjects, standards set for the conduct of the study, and restrictions imposed on the research

(i.e. sample size limitation or approval of only a part of the study). At the time of continuing review, the IRB must ensure that the research was conducted according to the contingencies described in the previously issued approval notice.

Approval for Follow-up Only

A research project approved for “follow-up only” occurs when subject accrual and research-related interventions have been completed, although previously enrolled subjects may continue to be monitored for safety and outcomes as detailed in the approved protocol. When approval for “follow-up only” is granted, the approved consent form(s) will not be issued.

Approval for Data Analysis Only

A research project approved for “data analysis only” occurs when subject accrual and all follow-up activities at UNTHSC have been completed. The protocol remains active for data analysis purposes only. Protocols should remain open for data analysis only when the investigator intends to continually analyze the data for potential dissemination through journal articles, poster presentations, etc., related to the stated objectives in the currently approved protocol.

IRB Application Withdrawal

A submission to the IRB will be withdrawn if the investigator’s response to IRB correspondence is not received within the time frame specified in correspondence sent to the investigator. If a response to the IRB correspondence is received after the specified time frame, and the research project originally underwent full board review, the project must return to the full board for review and approval. Additionally, a submission will be withdrawn if the investigator requests the IRB to discontinue review of the protocol before an approval notice has been issued.

In the event that a project sponsor or funding agency supporting the protocol permanently stops or closes a study, the principal investigator will follow Protocol Closure procedures (see below; also see Final Report).

Protocol Closure

A research project is closed when subject accrual, subject follow-up and data collection are completed at UNTHSC. Once the investigator or the IRB has closed a study, no further research interactions with subjects may occur. However, given the nature of scientific inquiry, data analysis may continue after a project is closed. However, investigators are still required to continue with sound ethical practices regarding data management and confidentiality of subject information and study documents.

5.17 IRB Review of Scientific Merit

Scientific inquiry is a continual process of rigorous reasoning supported by a dynamic interplay among methods, theories, and findings. It builds understanding in the form of models or theories that can be tested. IRB review of the scientific merit and research methods of a protocol is a basic expectation of the ethical review process and refers to the overall evaluation of ethics, risk benefit, reasoning, logic, goals, methods and hypotheses (if any). According to federal regulations, the IRB is required to review the scientific merit of proposals (45 CFR 46).

Scientific peer review of the study design, methods and scientific merit undertaken by a UNTHSC department, school, center or institute outside of the investigators “home” department/school or by a federal agency is, of course, helpful, but not solely the standard by which merit is evaluated. Federal agency guidelines note that the final and definitive assessment of scientific merit regarding an IRB approval is the IRB itself, and that such a scientific review cannot be solely delegated to another body.

The IRB reviews all studies to ensure that:

- The research uses procedures consistent with sound research design;
- The research design could allow the proposed research question to be answered;
- The potential risk/benefit relationship is acceptable;
- The purpose and specific aims are stated clearly, are feasible, and the research will contribute to generalizable knowledge.

Experts agree that the IRB should approve only research that is both valid (can answer the questions posed) and of value. OPHS, on behalf of the IRB, may request an expert consultant review a proposed research project or defer to scientific review committees in order to determine whether a study has sufficient scientific value (merit) and/or if a study design places subjects at unnecessary risk. Before the consultant reviews the study, OPHS will confirm with the consultant(s) that there is no potential conflict of interest.

How the Investigator Can Help the IRB in its Scientific Review

To assist OPHS and the IRB to evaluate the scientific merit of a given protocol, the Principal Investigator, through the protocol application and synopsis, should do the following:

- Write a clear, concise background and justification section in the protocol. Include discussions (with references) of why this research question is an important one to ask at this time in the understanding of the disease, condition, question or situation;

- Write a clear, concise methods section of the protocol, describing how the study question will be answered. Indicate how the data will be analyzed to answer the study question. Justify the number of human subjects that will be recruited in order to answer the study question;
- Thoroughly describe what the risks, harms and benefits to subjects are. Honestly assess whether and how the benefits are reasonable in relation to the risks (Hint: a simple restatement that the benefits outweigh the risks is not adequate!). Describe how subjects will be monitored to assure their safety and to be able to identify any harm that may occur. Include a description of the data safety and monitoring plan (if applicable);
- If the investigator believes that the IRB is lacking in expertise in a particular topic area, he or she should consider becoming a member of the IRB or recommend the use of a consultant.

In general, if the principal investigator is concerned that the IRB may not be familiar with or aware of the special aspects of the proposed research activity, methodology, techniques, etc. it is the PI's responsibility to provide sufficient, clear and compelling information to advise and educate the Board in order for it to review and effectively evaluate the protocol.

Additional Considerations:

Use of Consultants

Consultants will be used for biomedical or social and behavioral research review when the Board lacks sufficient expertise in the area being researched and the risk level warrants it.

Chapter 6: Submitting the Application to the IRB: Forms and Process

CHAPTER CONTENTS

- New IRB Application (Exempt, Expedited, Full Board)
- Just-in-Time Processing of Human Subject Protocols
- Progress Report (Continuing Review/Final Report)
- Exempt Category Review
- Application Processing
- Communications from the IRB
- Reporting in Writing-Findings and Actions to the Investigator and the Institution
- Limitations on IRB-Approved Studies
- Appeal of IRB Decisions by the Investigator
- Other Committees Within the University Reviewing Human Subjects Research
- Acceptance of IRB Approval From an Outside Institution

Overview

This chapter discusses the intricacies involved with the IRB application and process. It also explains the application process and the communications from the IRB to the investigators. It defines reviews by other university committees and the role of the investigator when applying for an IRB approval from an outside institution.

The IRB expects the investigator to respond to all items on the IRB application. The application must provide sufficient detail to evaluate the study's purpose and/or procedures. OPHS staff are available to respond to questions by e-mail or phone. Investigators with unique situations are encouraged to contact the OPHS and/or IRB Chairperson. Upon request and resources permitting, the OPHS will review applications and/or Informed Consent forms in the developmental stage, prior to actual submission.

NOTE: Since IRB and OPHS forms are subject to change, often as a result of changes in regulations or federal guidance, please consult the UNTHSC OPHS web site for latest versions of these forms, along with related instructions and suggestions.

6.1 New Research Study Review Form (also known as the IRB Application):

Investigators will complete an Exempt, Expedited, or Full Board IRB Application for each new protocol submission.

Only signed applications will be accepted. The application should be signed by the Principal Investigator, the Student Investigator (s) (if relevant), and the Department Director (only if required by that department).

UNTHSC student investigators must designate a faculty member as the Principal Investigator for their IRB application. The IRB will not honor the signature of anyone other than the authorized signers (no “per” signatures).

Investigators must carefully address each required item in the application. The application must be complete prior to submission.

Items Required by the IRB for a New Protocol Submission

1. IRB application form (Exempt, Expedited, or Full Board depending upon the type of project);
2. Protocol synopsis (using UNTHSC format as described on the website) for Expedited and Full Board protocols;
3. Informed Consent or other consent documents (research statement, cover letter, oral consent script, etc) as appropriate. If using a ‘sponsor’s’ template for the Informed Consent form, it should be modified to include UNTHSC’ IRB informed consent standard language and headings;
4. A HIPAA Authorization for studies that involve protected health information (PHI)-see Section 9.8 for specific information;

5. When appropriate, a HIPAA Research Waiver form for research studies where it is not feasible to obtain Authorization from the research subjects (see Appendix C);
6. When appropriate, a Waiver of Informed Consent form or Waiver of Documentation of Informed Consent form (see Appendix C);
7. Recruitment materials (including brochures, flyers, advertisements, audio tapes, video tapes, or letters to potential subjects) that will be used to inform people about the study.
8. Questionnaires, survey instruments, stimuli, etc., that will be used in the study.
9. Other Items such as phone and verbal scripts for situations that involve providing information to potential subjects via telephone or in person, as well as texts of emails or website postings.
10. Signed Conflict of Interest Disclosures for each listed key personnel (Expedited and Full Board protocols only);
11. Verification of human subjects training for all key personnel: submit hard copies of certificates if evidence of such training is not already on file with OPHS;
12. A copy of the complete funding agency grant proposal, including budget pages and appendices (if applicable); for clinical trials, attach a copy of the sponsor's contract;
13. Investigator's CV;
14. Other forms, such as a HIPAA Compliance Data Use Agreement, when applicable.

For clinical trials:

- Investigational Drug or Device Brochure. If the study involves an investigational drug or device, a copy of the investigator's brochure must be provided. If the study involves an investigational drug, include documentation of the Investigational New Drug (IND) number from the sponsor (if not indicated on the investigator's brochure or protocol), or, in the case of investigator-held INDs, a copy of the FDA letter that informed the PI of the IND number.
- The industry-sponsored clinical protocol, or full protocol (if applicable).

For studies involving physicians or procedures requiring a physician:

- A photocopy of the medical license of each participating physician (MD, DO, DPM, etc.)

6.2 Processing of a NEW Application

Screening IRB Applications and Investigator Responses

All IRB applications and investigator responses are screened by OPHS staff. If the application is incomplete it will be returned to the Principal Investigator, and/or additional information will be requested via phone or e-mail. Investigator responses are reviewed for completeness and then forwarded to the appropriate person (see below) for assignment for either full board review, expedited review, or exempt status. Once the complete application is submitted, it is assigned an IRB number. The IRB number remains with the study until the study is closed. The IRB number should be used by both OPHS and the Investigator on all relevant protocol correspondence.

Just-in-Time Processing of Human Subject Protocols

Human subject research protocols do not need to be submitted for review until the project is likely to be activated. A significant percentage of planned research project protocols submitted to the OPHS and IRB end up never activating (internal funding insufficient, external grant application unfunded, research team changes focus, etc.). Another group of protocols are reviewed, but the project might languish for months or years before it gets underway, if ever. All of this generates substantial lost investigator and staff time and misallocation of scarce resources, particularly in a time of increased research activity and a need for thorough protocol review.

In order to meet these challenges, and to assure timely and effective review as required by federal regulations, the OPHS and IRB employ a “Just In Time” review system. Many sponsors and funding agencies employ similar systems, in which they require verification of IRB review and approval only if that agency plans to fund the proposed research activity. This “Just-In-Time” approach will also decrease investigators’ workloads and save time and resources of research teams, since applications for IRB review will be needed only when there is a high likelihood of funding and/or project initiation.

For EXTERNALLY funded projects (sponsored by NIH, NSF, CDC, ED, DOE, pharmaceutical or device company clinical trials, etc.): *Full Board Protocols will be reviewed ONLY when the Principal Investigator provides the following documentation (Note that protocols lacking this information will be returned without review):*

- *Notification from the funding agency (usually an official agency document) indicating that funding is likely or imminent.* Typically this involves a summary score from the review panel or program officer indicating a high probability of funding to initiate the project, a request

for a just-in-time process to begin, or a signed contract authorizing the project.

- Some agencies, foundations or sponsors require IRB approval at the time of proposal submission. In those cases, an application for IRB review must include *documentation from that sponsor clearly stating the sponsor's requirement that IRB approval must be obtained before submission of the proposal*. Typically this would be stated in the sponsor's guidelines, website, or other published information. Email statements or other personal correspondence is insufficient documentation of this requirement.
- *Clinical Trials protocol applications* for review (those that are not funded through federal agencies) should provide a *copy of the contract cover sheet indicating projected start date* for the proposed trial activity.

Currently, the IRB meets once per month. A properly prepared and documented application and protocol can be effectively approved promptly and in time to meet funding or sponsoring agency requirements.

For NON-EXTERNALLY funded projects (UNTHSC internal funding sources, investigator-initiated non-funded research, etc.):

- Investigators are encouraged to submit applications for IRB review *only when there is a high likelihood of the project beginning* soon after IRB review and approval. OPHS and the IRB work to provide timely and effective reviews of all application and protocols, so there is no need to “bank” or initiate IRB reviews for projects planned for the distant future.

IRB Review

The IRB Chair, Vice Chair, or Director of OPHS, or designee determines whether the project is eligible for exempt status (OPHS staff may also make this determination with confirmation by the IRB Chair, Vice Chair or designee), expedited review, or requires full board review. If exempt or expedited review is appropriate, the IRB Chair, Vice Chair, or OPHS Director, designee, or OPHS staff may request additional clarification or materials in order to determine final approval.

All new and previously considered (but not yet approved) proposals submitted to OPHS that are neither exempt nor eligible for expedited review will undergo full board review by a quorum of members at a fully convened meeting. Any IRB member with a conflict of interest on that protocol will leave the room prior to any discussion and vote on that proposal. If the

remaining IRB members have a question, the IRB member/alternate with the conflict of interest may be invited to return to answer a question, but then must again leave prior to further deliberation and the committee vote.

If the IRB invites an investigator to a committee meeting to address questions, the investigator will address the questions and then leave the room before the committee continues its discussion, deliberation and vote.

Required Revisions by the IRB Prior to Final Approval

For studies that are classified as exempt or expedited, the investigator must satisfactorily respond to all requests from the Chair, Vice Chair, Director (OPHS) or IRB designee. If the reviewer and the investigator cannot agree on the changes required to secure approval, the application is sent to a convened IRB for review. The Chair, Vice Chair, and/or IRB designee may approve projects as submitted or require modifications prior to approval. When the Chair, Vice Chair, and/or IRB designee determines the study is procedurally sound and all requested revisions have been made, they approve the project.

If the project is Exempt, a letter of approval declaring that protocol is Exempt from IRB review is sent to the Investigator by OPHS staff after consultation with the IRB Chair, Vice Chair or OPHS Director or designee.

If the protocol meets criteria and is approved under Expedited Review, the Chair, Vice Chair, and/or IRB designee will certify the project as such, send a Board Action and letter of approval to the PI and indicate the approval period and need for Continuing Review.

Note that the Chair, Vice Chair, and/or IRB designee are not empowered to disapprove projects; in such cases the application is forwarded for full board review along with the comments and recommendations of the reviewer(s).

For studies that require full board review, the investigator receives written notification (Board Action) that describes relevant IRB determinations regarding their study submission. If the Board Action indicates that the study has been approved pending receipt of the specific non-substantive revisions, the IRB Chair, as directed by the Board during that convened meeting may review and approve the submitted revisions.

If the convened IRB requests substantive clarifications or modifications that are directly relevant to the determinations required by the IRB under the regulations, the study will be **deferred** pending receipt of additional clarifications and modifications. Once the clarifications are submitted the deferred study will be scheduled for review by the full board at a subsequent meeting.

The goal of both the OPHS and the IRB is to work with the investigator to ensure that human subjects are protected in such a way that the project ultimately may be approved. A project may be disapproved by a full board and the minutes will specify the reason(s) for disapproval. The investigator may respond in /person and in writing to a decision of disapproval.

6.3 Communications from the IRB

Communication to the Investigator Conveying IRB Decisions:

The Principal Investigator (PI) is the key recipient of all OPHS and IRB communications. If requested by the PI in writing (or via email), OPHS will also send copies of OPHS communications to a designated person defined by the PI. For example, the designee may be a Co-Investigator, study coordinator, research assistant, student investigator, administrative or executive assistant, etc. However, no matter whom the PI may designate as recipient of communications, the Principal Investigator continues to be fully responsible for all actions associated with the protocol, including acting on all OPHS and IRB correspondence.

Following an OPHS or IRB action, the PI is sent a written Board Action or letter notification of IRB determinations (e.g. approval, required modifications/ contingencies, deferral, disapproval, termination, approved consent documents and flyers, etc.).

Approved

An approved action from the full board, Chair, Vice Chair, or IRB designee means the study as submitted is approved and no conditions are required. When the study is approved, investigators may initiate the research, subject to any regulatory agency mandated delay.

Accepted with Contingencies

When a study is accepted with contingencies, the investigator must satisfactorily address the contingencies before final approval of the study can be given. The study cannot be initiated until the IRB Chair, Vice Chair, or IRB designee has reviewed the investigator's response to the contingencies and gives final IRB approval. In some cases, the investigator's response may require subsequent review by a convened full board. OPHS will forward correspondence to the investigator requesting clarification of minor points and/or modifications to the protocol or Informed Consent form. Once all of the conditions are met, the study may be approved.

Deferred

A study can be deferred (tabled) by the full board, Chair, Vice Chair, and/or IRB designee for several reasons, including:

- Insufficient information was provided by the investigator;
- Document changes were not tracked as required by the IRB;
- The IRB requests substantive clarifications or modifications that are directly relevant to the determinations required by the IRB under the regulations;

- Significant changes are required that cannot be solely addressed by the IRB Chair and must be re-visited by the Full Board.

If a study is deferred, additional information must be provided by the investigator as deemed necessary. Studies are deferred when the IRB has substantive concerns or significant requests for clarification.

Disapproved

If the full board finds the protocol unacceptable, usually because the risks far exceed the benefits or because of potential harm to subjects, the protocol and informed consent will be disapproved. The investigator will be informed in writing of the reasons for disapproval and may resubmit their study application after making the recommended changes. Additional information must be provided by the investigator as deemed necessary by the full board. The magnitude of changes is typically extensive requiring study redesign and re-reviews by the full board. Examples of changes include addressing concerns regarding subject safety, extensive study re-write, and other issues deemed necessary by the full board. Many protocols have been approved after such changes have been made.

Communication to the Institution Administration Conveying IRB Decisions:

OPHS reports IRB determinations by sending minutes of the fully-convened IRB meetings and expedited review minutes electronically to the IRB Board Members, the UNTHSC Institutional Official (VP for Research), and the Director of the Office for the Protection of Human Subjects (OPHS) .

Communication to the Sponsor of Research:

The sponsor/funding agency of the research receives the IRB determination letter directly from the investigator.

In some situations (such as study suspension for risk-related cause or protocol violations) and where required by law and/or the sponsor, OPHS will notify the sponsor of any appropriate IRB action involving suspension, disapproval or termination of approval for a protocol.

6.4 Limitations on IRB-Approved Studies

An approved study is limited to the recruitment activities and study procedures that were described in the initial application. If the investigator wishes to change the study recruitment activities or procedures, an amendment application must be submitted for IRB review.

6.5 Approval Period

Federal regulations specify that each study can only be approved for a maximum of one calendar year and that research activities may not continue beyond that date without IRB approval (continuing review/progress report). The IRB Board Action and Notice of Approval

indicates the due date for the next continuing review. The IRB may review the project more often than once per year depending on the level of risk. Only a current IRB-approved Informed Consent form may be used to enroll subjects.

6.6 Appeal of IRB Decisions by the Investigator

The UNTHSC IRB is committed to working with investigators to solve problematic issues with study design, recruitment, and procedures so that the IRB can **approve** the research study. The IRB may conditionally approve a research project pending specific required changes in procedures or in the Informed Consent form. If the IRB decides to **disapprove or defer** a research activity, it shall include in its written notification a statement of the reasons for such a finding. The investigator may appeal the disapproval or deferral to the IRB in writing. The investigator should provide a rationale for the appeal and any other relevant supporting documentation. The response will be considered at the next respective convened IRB meeting. The investigator may be invited to attend the IRB meeting to answer questions or provide additional information. The IRB will notify the investigator in writing of the decision.

In the case of a decision by the IRB to defer, disapprove, suspend, or terminate a project, the decision may not be reversed by any other official of UNTHSC.

For more information on the appeal process see Chapter 19.

6.7 Other Committees within the University Reviewing Human Subjects Research

Research approved by the IRB may be subject to review and approval or disapproval by other university committees. While research approved by the IRB may be subject to further review and approval or disapproval by these and other committees, the research project involving human subjects, even if approved by these committees, cannot go forward until it has been approved by the IRB.

6.8 Acceptance of IRB Approval from an Outside Institution

Section modified on 8/10/10 regarding the use of commercial IRBs.

Section modified on 9/9/11 regarding including a list of key personnel for projects utilizing a commercial IRB.

The investigator is responsible for submitting an application to the UNTHSC IRB for review and approval, along with documentation from the outside research sites IRB, Ethics Review Committee equivalent or official approval from the outside research site.

In special situations, UNTHSC may authorize review by another IRB that is listed under the UNTHSC FWA through an Institutional Review Board (IRB)/Independent Ethics Committee

(IEC) Authorization Agreement signed by the UNTHSC Institutional Official and in accordance with the special terms of that Authorization Agreement. This includes the use of commercial (so-called “central”) IRBs.

Note that The IRB will only accept approvals from sites with a Federalwide Assurance (FWA) or its equivalent and only with the prior approval of the UNTHSC Institutional Official.

The use of a commercial (for-profit) IRB by UNTHSC investigators needs to be approved by the FWA Institutional Official on a case-by-case basis.

In addition, UNTHSC requires that various documents and reports be submitted to the UNTHSC IRB by the local (UNTHSC) Principal Investigator as follows:

- Principal Investigator reports the following to the UNTHSC Office for the Protection of Human Subjects (OPHS) within ten (10) working days of receipt of documents by the Principal Investigator or submission by the PI to the commercial IRB, as appropriate:
 1. Copy of the commercial IRB Initial Approval Letter, including protocol and consent documents associated with the study;
 2. Complete list of all UNTHSC key personnel (faculty, staff, and students) associated with the protocol. This list to be updated within ten (10) working days of adding personnel to the project.
 3. Copies of all FDA Form 1572 for UNTHSC personnel associated with the protocol; again, updated within ten (10) working days as appropriate.
 4. Copies of Continuing Review (Progress Reports) submitted to the commercial IRB;
 5. Copies of the commercial IRB Continuing Review approval letters;
 6. All **on-site (UNTHSC)** Serious Adverse Events (SAE's) associated with the study;
 7. All monitoring and audit reports from sponsor, regulatory and administrative agencies;
 8. Notice of closure of the trial.

The IRB Chair, when deemed necessary, will communicate with external sites. See Appendix F (Written Agreement for Delegation of IRB Review to Non UNTHSC IRB) for examples of documentation that will be required when using an "off-site" IRB.

Chapter 7: Reporting Requirements After IRB Approval

CHAPTER CONTENTS

- Modifications/Amendments/Revisions-Changes in Research After Initiation
- Continuing Review
- IRB Approval Has Expired
- Defining and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (Serious/and or Unexpected)
- Protocol Exceptions
- Project Closure
- Publishing When Data is Collected For Nonresearch Purposes

Overview

This chapter describes IRB-related reporting requirements of an investigator after a research project is initiated. It covers amendments of approved research, continuing review requests, expiration of IRB approval, unanticipated problem reports, study closure, record keeping, and publication. Only the major reporting responsibilities of investigators are described here. There may be additional responsibilities placed on the Principal Investigator (PI) by a funding agency, other regulatory agencies, or the IRB.

7.1 Modifications/Amendments/ Revisions - Changes in Research after Initiation

Section updated on 10/19/10 (clarification on OPHS staff approval of minor/non-substantive changes to Exempt category research).

The IRB requires investigators to submit written requests to OPHS for modifications to IRB approved studies, including any modifications to Exempt research studies. The OPHS uses the expedited review procedure to assist the IRB with review of minor changes in previously approved research during the period covered by the original approval for Expedited or Full Board protocols. Approval for a minor/non-substantive modification to an Exempt category research project can be made by OPHS staff and verified by the OPHS Director. When a proposed change in a research study is not minor (as defined in accordance with 45 CFR 46.110), the IRB will review the proposed change at a fully convened board meeting. IRB approval must be granted before any changes can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects or others. In such a case, the investigator must promptly inform the IRB of the change. The IRB will review the change to determine that it was consistent with ensuring the subjects' continued welfare. The approval notice sent to the investigator outlines this responsibility.

Minor modifications (such as title changes, changes in investigators, changes in contact information in the protocol and consent form, formatting changes, etc.) may be approved using the expedited IRB review procedure, or may be made by OPHS staff and verified by the OPHS Director if the project was approved as exempt category research and the modification does not change the level of review required. More extensive modifications may require full board review if those modifications increase risk to subjects. Revisions or clarifications may be required from the investigator.

The original expiration date of a study does not change when an amendment is approved by the IRB.

The Principal Investigator will submit to the IRB via OPHS a *signed* memorandum clearly describing and justifying the modifications/amendments to the protocol along with any potential risk/benefit information.

In addition, the Principal Investigator will submit the following with the cover letter:

- Revised version of Protocol using a “track changes” feature (or other electronic means of highlighting the changes without eliminating original text)
- Revised version of Consent Document(s) using a “track changes” feature (or other electronic means of highlighting the changes without eliminating original text)
- Other documents related to the protocol modification
- Clean (un-highlighted) versions of the revised Protocol and modified Consent Document(s) suitable for re-stamping by OPHS (“IRB Approved” stamp)

See Section 5.7 for additional information on how to compile amendment submissions.

7.2 Continuing Review (Progress Report)

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, and not less than once a year 45 CFR 46.109(e), after the study receives initial IRB approval. Subsequent IRB review is called "continuing review" (or Progress Report). If a project initially received expedited review and no additional risks have been identified, the continuing review may receive expedited review. If a project initially received full board review, the project generally requires full board continuing review unless the IRB determined otherwise at that initial review.

It is the Principal's Investigator's responsibility to know when a continuing review (Progress Report) is due and to seek continuing review and approval in a timely manner. The date when such a review is due (and expiration date) are clearly noted on all initial approval letters and Board Actions.

To assist the PI with timely progress reports, whenever possible, OPHS will send to the PI a reminder notice indicating when such a report is due, and the quantity and types of documents needed for review.

Typically, such notices will be sent one to two months in advance of the protocol approval expiration date.

Investigators are encouraged to submit the continuing review application in a timely manner (as described in the Request for Continuing Review notice) before the study expiration date to allow for timely continuing review and approval. It is the PI's responsibility to submit a complete and accurate application for continuing review in sufficient time to permit the IRB to review and approve the application prior to its expiration date.

NO HUMAN SUBJECTS ACTIVITY MAY TAKE PLACE AFTER THE EXPIRATION DATE unless there is an overriding safety concern. If the study has expired, the investigator must submit a request for approval to continue subjects currently on the trial and to continue data analysis (contact OPHS for more information).

Continuing review information must be submitted to OPHS using a continuing review application (Progress Report Form). The IRB expects the investigator to respond to all items on the continuing review application (progress report). Incomplete applications may be returned to the investigator. In its continuing review function, the IRB will pay special attention to determining whether new information or unanticipated risks were discovered during the research. The IRB will require that any new information relevant to the subjects' participation be provided to the subjects. The IRB will review the current informed consent document to determine whether the information contained in it is still accurate and complete, and whether new information obtained during the course of the study needs to be added.

Progress Report / Continuing Review Application

Continuing review applications must include the following information as outlined in the Progress Report Form:

1. The number of subjects entered into the research study in total and during the reporting period and how many additional subjects will be entered;
2. Number of withdrawals from the research and the reasons for withdrawals;
3. A summary description of adverse reactions, interim findings and amendments or revisions made since the last continuing review;
4. A current potential risk /benefit assessment based on study results;
5. Any new information relevant to any subject's participation since the IRB's last review;
6. Any relevant multi-site trial reports;
7. Copies of the current informed consent form(s) in the original study application;
8. Copies of the currently-approved Protocol Synopsis;
9. Current Conflict of Interest disclosures for all key personnel.

The number of copies to be submitted to OPHS will vary according to study and size/make-up of the IRB and will be specified by OPHS at the time of the Progress Report request (see Chapter 5 for more details).

7.3 IRB Approval Has Expired

If the investigator does not submit a complete and accurate continuing review application (progress report) in time for an effective review by the IRB, the approval period may expire. In the event that the approval period expires, both the investigator and the department Chair or Dean are notified by e-mail and in writing that IRB approval period has lapsed. The email includes a notice that **no human subject research** may be conducted, including recruitment, enrollment, interventions, or interactions until IRB approval is obtained. If the study has expired and human subjects are currently receiving the study treatment, the investigator should immediately contact the IRB to permit continued treatment of these subjects and follow-up activities(see Section 7.5). The IRB Chair or Vice Chair determines whether it is in the best interest of each subject to continue in the study and provides this determination to the investigator.

In certain situations, the IRB may be required to report to the appropriate sponsor or funding agency that protocol approval has lapsed, and such reporting will be made directly by OPHS and the IRB Chair.

7.4 Defining and Reporting Unanticipated Problems Involving Risks to Subjects or Others, and Serious Adverse Events or Unexpected Events

This section was updated on 1/26/11 to address summary reports of SUSARs and SAEs.

The term unanticipated problems (involving risks to subjects or others) and the term adverse events (serious and/or unexpected) can often be confusing to researchers, IRB members, and OPHS staff. The reason both are used and have different meanings and reporting requirements is that they come from different regulatory bodies.

Unanticipated problems involving risks to subjects or others is from the Office of Human Research Protections OHRP/The Common Rule 45 CFR 46.103(b)(5) and *adverse events* (AE) are from the Food and Drug Administration (FDA) Information Sheets: Continuing Review After Study Approval:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm115834.htm>

Defining Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem involving risks to subjects or others is any untoward event that is unanticipated, occurs in any aspect of a research study, and includes anyone directly or indirectly involved in a study. Refer to the definitions table and reporting of unanticipated problems and adverse events chart at the end of this chapter. The following are a few examples of **unanticipated problems** involving risk to subjects or others:

- PI's laptop, data drive, storage device is stolen or missing, and it contains confidential research data about subjects.
- PI is charged with a felony related to the study.
- Spousal abuse for participating in a study.
- Subject becomes pregnant in a study that poses a risk to the fetus.
- Any complaint of a subject that indicates an unanticipated risk or which cannot be resolved by the research team.
- Any other event that, in the opinion of the investigator, constitutes an unanticipated risk or problem.

Any unanticipated problem listed above requires reporting to the IRB even after the subject has completed the study or after the subject has withdrawn from the study, until the study is

closed. Most unanticipated problems involving risks to subjects or others are not considered to be Adverse Events. However, some unanticipated problems overlap with adverse events (see the diagrams at the end of this chapter).

Reporting Unanticipated Problems Involving Risks to Subjects or Others

Investigators are required to submit to the IRB, a detailed written report describing the unanticipated problem involving risks to subjects or others. Prompt reporting to the UNTHSC IRB promptly, not to exceed ***ten (10) working days*** of the investigator's knowledge of the unanticipated problem, is required.

Unanticipated Problems are reported by narrative letter. There is no standard OPHS or IRB Form for reporting Unanticipated Problems.

Defining Serious Adverse Events and/or Unexpected Events

Adverse events are defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events are defined as being serious if the event adversely alters the relationship between risks and benefits and includes events that either result in or require intervention to prevent:

1. Death
2. Life-threatening situations;
3. Hospitalization or prolongation of hospitalization;
4. Severe or permanent disability (either physical or psychological);
5. Congenital anomaly/birth defect;
6. Pregnancy. Note that pregnancy does NOT have to be reported if the subject is receiving follow-up only, and conception occurred outside of the time period that the study protocol requires contraception (e.g. contraception is required for 6 months after the last dose of the study drug).

Reporting of Serious Adverse Events – Internal or “On-Site” SAEs

Serious Adverse Events (SAEs) must be reported to the IRB using the appropriate OPHS Form (see website for versions of forms). Reporting to the IRB must be prompt, not to exceed ***ten (10) working days*** of the investigator's knowledge of an event is required. This reporting requirement includes adverse events that are unanticipated problems (see diagram at the end of this chapter), injuries, side effects, deaths and other problems occurring at UNTHSC, or other

locations in which an investigator is responsible for the conduct of the research **and** the UNTHSC IRB serves as the IRB of record.

On-Site adverse events are those events that occur within the institution and Off-Site adverse events occur at other institutions (reported to the investigator by the sponsor). Based upon the reportable event, the IRB may need to reconsider its approval of the study, require modifications to the study or revise the continuing review timetable. Also see the specific instructions for reporting internal adverse events and external adverse events below.

For studies that involve drugs, devices, biologics or interventions, the IRB requires the investigator to report the following:

On-Site: For Subjects Enrolled by UNTHSC Investigators

The investigator must report a Serious Adverse Event to the IRB if it is serious, unexpected, and related or possibly related to the study. [Note – Both the "serious" and "unexpected" definitions stipulate that the SAE is *associated with the use* of the drug/device/intervention. If the PI believes that the SAE is *not related* to the drug/device/intervention, it may still need to be reported to the IRB. See the end of this chapter for definitions.

Off-Site: For Subjects Enrolled at Other Sites by Non-University Investigators

In multi-site trials, investigators are required to report to the IRB SAEs that occur in subjects enrolled elsewhere (i.e., by non-University investigators) **only** when the adverse experience is BOTH serious AND unexpected AND associated with the use of the drug/device. [Note – Both the "serious" and "unexpected" definitions stipulate that the SAE is *associated with the use* of the drug/device/intervention. If the PI believes that the adverse experience is *not related* to the drug/device/intervention, it should not be reported to the IRB. Refer to the *External Adverse Event Reporting* policy and flowchart below.]

SAEs and/or unexpected or unanticipated problems meeting the above definitions are generally reviewed by the IRB chair (some may require full board review). Investigators are notified of the review through OPHS. SAEs in subjects that are serious and unexpected and probably or definitely related to the drug/device/ treatment automatically require full board review. SAEs at other sites that are serious, unexpected, and possibly related to the drug/device/intervention or change the potential risk/benefit ratio or require changes to the Informed Consent Form or protocol, automatically require full board review. If the Informed Consent Form is required to be revised, the IRB may also require that all current and previous subjects be re-consented. The IRB Chair, at his or her discretion, may refer any other SAE to the full board for review. [Note that clinical trial sponsors always require re-consenting of current subjects.]

If a sponsor requires the PI to report to the IRB SAEs that do not meet the above criteria, the investigator should do so. Reports that do not meet these criteria will be “filed” in the protocol file folder and acknowledged as received and reviewed by the IRB Chair.

In Multi-center research, the PI is responsible for communication with the sponsor of the research as necessary. The sponsor should report to the PI, any relevant information from external sites conducting the same study.

Note that if the sponsor reports to a UNTHSC investigator any serious adverse event, whether it is deemed unanticipated or not unanticipated by the sponsor, that event must be reported to the IRB for acknowledgement and review. All reports from the sponsor regarding serious adverse event must include a copy of whatever sponsor correspondence accompanied the report.

Serious Adverse Events (SAE) submissions can include: any associated materials such as medical record notations or reports with the name and medical record number of the individual redacted, an amendment to the protocol indicating changes associated with the event or problem, study related events that **do not** occur at UNTHSC or other locations in which the investigator is responsible for the conduct of the research **and** the UNTHSC IRB does not serve as the IRB of Record (submit these in summary format at the time of continuing review). If the sponsor or the DSMB has determined that the study-related event changes the potential risk /potential benefit profile, the events must be reported to the IRB immediately. In these instances, the event should be reported as an amendment to the IRB approved proposal.

The investigator is responsible for the accurate documentation, investigation, and follow-up of all SAE's that occur at the site in which the investigator is responsible for the conduct of the research.

Off-Site Serious Adverse Event (SAE) Reporting

An Off-Site Serious Adverse Event is an event that occurs in a non-UNTHSC participant that has been reported to the UNTHSC investigators. In multi-site trials, investigators receive safety reports from the sponsor, including Investigational New Drug (IND) Safety Reports and MedWatch Reports. Such reports are considered Off-Site Serious Adverse Event reports.

Off-Site Serious Adverse Event reports must be submitted to OPHS for IRB review within 10 working days of receipt by the local (UNTHSC) investigator.

SAE Reports to the IRB (via OPHS) must be signed by the Principal Investigator, or in the case of FDA-relevant project (for example, clinical trials) by someone designated on the protocol's FDA Form 1572 (Principal Investigator, Sub-Investigator, Co-Investigator, etc.).

Based on current major international guidance documents addressing the reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs), the reporting of these events to the UNTHSC IRB prescribe that "off-site" investigators must report all SAEs and SUSARs *immediately to the sponsor* who is then responsible for their prompt notification to the local (UNTHSC) Principal Investigator. The UNTHSC Principal Investigator, in turn, is obligated to report these events to the IRB.

Summary Reports of “Off-site” SAEs and SUSARs

In some cases, at the sponsor’s initiation, such “off-site” SAEs or SUSARs may be periodically reported (quarterly, annually, etc.) as a line listing, accompanied by a brief report by the sponsor highlighting the main points for concern and noting any changes increasing the risk to subjects and any new issues adversely affecting the safety of subjects. Such reports should be reported to the IRB within 10 working days of receipt from the sponsor with an accompanying statement from the local (UNTHSC) Principal Investigator regarding any changes increasing the risk to subjects and any new issues adversely affecting the safety of subjects. The objective of such a “grouping” or “bundling of off-site SAEs and SUSARs is to replace the current practice of sending large numbers of individual case reports to IRBs with a more reasonable approach, namely periodic and ad hoc communications to investigators and ethics committees that include regular updates of important safety information as well as the evolving potential risk/benefit ratio profile and highlights of important new safety information.

However, note that such periodic reporting of SAEs and SUSARs cannot replace the need for a close monitoring of adverse events and significant new safety information. Occasionally, a single case report, that has implications for the conduct of the clinical trial or that warrants an immediate revision to the informed consent, must be communicated to the IRB within the 10-day window described above. Again, if the sponsor or the DSMB has determined that the study-related event changes the potential risk/benefit ratio profile, the event must be reported to the IRB immediately.

For practical operational purposes, whenever a summary report of off-site SAEs and SUSARs arrives *from the sponsor*, it shall be processed and reviewed as a single IRB event and report.

Also note that a UNTHSC Principal Investigator is not allowed to “bundle” or “group” individual off-site SAE or SUSAR reports into a summary report. Such summary reports can only be initiated and arrive from the sponsor or DSMB. If SAEs and SUSARs arrive as individual reports, they must be reviewed by the UNTHSC Principal Investigator and reported to the UNTHSC IRB as single, individual and separate reports.

Definitions of Serious Adverse Events (SAE) and Unanticipated Problems (UP)

Off-Site Serious adverse events:	Serious Adverse events (SAEs) experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the UNTHSC IRB has jurisdiction
On-Site Serious adverse events:	SAEs experienced by subjects enrolled at the site(s) under UNTHSC IRB's jurisdiction.
Reasonably related:	An event is defined as reasonably related to the research if it is more likely to be caused by the research procedures than not.
Serious Adverse Event (SAE):	<p>An event is defined as being serious if the event adversely alters the relationship between risks and benefits and includes events that either result in or require intervention to prevent, for example:</p> <ul style="list-style-type: none"> ▪ Death ▪ Life-threatening situations; ▪ Hospitalization or prolongation of hospitalization; ▪ Severe or permanent disability (either physical or psychological); ▪ Congenital anomaly/birth defect; ▪ Pregnancy. Note that pregnancy does NOT have to be reported if the subject is receiving follow-up only, and conception occurred outside of the time period that the study protocol requires contraception (e.g. contraception is required for 6 months after the last dose of the study drug).
Unanticipated Problems (UP) involving risks to subjects or others:	Any event that is unanticipated at the time of its occurrence, is serious (adversely alters the relationship between risks and benefits of the research) and is related (likely to have been caused by research procedures).
Unexpected adverse event:	An event is defined as being unexpected if the event exceeds the nature, severity, or frequency described in the protocol or the investigator's brochure or if the event is not described in the protocol or the investigator's brochure.

UNTHSC Guidance on On-Site Serious Adverse Event (SAE) Reporting

The FDA defines a serious adverse event (SAE) as any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, a serious adverse drug or device event includes any experience that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, results in a congenital anomaly/birth defect, or may be classified as an important medical event (requiring medical or surgical intervention).

Within 10 working days of notification of the event, a detailed written report (IRB Form 3a – Serious Adverse Event Report for SAEs at UNTHSC) must be completed and forwarded, along with supporting documentation, to OPHS.

If the event resulted in death (regardless of whether the event is initially assessed as related to the study), or if the investigator initially assesses the SAE as ***possibly related (or greater causality)*** to the study protocol, an e-mail must also be sent to OPHS within **24 hours** of notification of the event. This e-mail must contain the following information:

IRB Project #
Principal Investigator
Project Title
Subject's Initials, Gender and Age
Date and Time of Event
Brief Description of Event
Investigator's Initial Assessment of Relationship of SAE to the Study
What Event Resulted In: Death
Life-Threatening Situation
Hospitalization or Prolonged Hospitalization
Severe or Permanent Disability
Congenital Anomaly/Birth Defect
Pregnancy*
Other (Important Medical Event)

* Note: Pregnancy does NOT have to be reported if the subject is receiving follow-up only, and conception occurred outside of the time period that the study protocol requires contraception (e.g. contraception is required for 6 months after the last dose of the study drug).

Federal Agency (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

This guidance represents OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

Date: January 15, 2007

Scope: This document applies to non-exempt human subjects' research conducted or supported by HHS. It provides guidance on HHS regulations for the protection of human research subjects at 45 CFR part 46 related to the review and reporting of (a) unanticipated problems involving risks to subjects or others (**hereinafter referred to as unanticipated problems**); and (b) adverse events. In particular, this guidance clarifies that only a small subset of adverse events occurring in human subjects participating in research are unanticipated problems that must be reported under 45 CFR part 46. The guidance is intended to help ensure that the review and reporting of unanticipated problems and adverse events occur in a timely, meaningful way so that human subjects can be better protected from avoidable harms while reducing unnecessary burden.

The guidance addresses the following topics:

- I. What are unanticipated problems?
- II. What are adverse events?
- III. How do you determine which adverse events are unanticipated problems?
- IV. What are other important considerations regarding the reviewing and reporting of unanticipated problems and adverse events?
- V. What is the appropriate time frame for reporting unanticipated problems to the institutional review board (IRB), appropriate institutional officials, the department or agency head (or designee), and OHRP?
- VI. What should the IRB consider at the time of initial review with respect to adverse events?
- VII. What should the IRB consider at the time of continuing review with respect to unanticipated problems and adverse events?

VIII. What should written IRB procedures include with respect to reporting unanticipated problems?

Additional OHRP guidance on this topic can be found at the end of this section, including:

- Glossary of Key Terms
- Examples of Unanticipated Problems that Do Not Involve Adverse Event and Need to be Reported under the HHS Regulations at 45 CFR Part 46
- Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR 46
- Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported under the HHS Regulations at 45 CFR Part 46

NOTE: For some HHS-conducted or -supported research, the Food and Drug Administration (FDA) and the HHS agency conducting or supporting the research (e.g., the National Institutes of Health [NIH]) may have separate regulatory and policy requirements regarding the reporting of unanticipated problems and adverse events. Anyone needing guidance on the reporting requirements of FDA or other HHS agencies should contact these agencies directly. Furthermore, investigators and IRBs should be cognizant of any applicable state and local laws and regulations related to unanticipated problems and adverse events experienced by research subjects, as well as foreign requirements for research conducted outside the United States. OHRP recommends that investigators and IRBs consult with their legal advisors for guidance regarding pertinent state, local, and international laws and regulations.

Target Audience: IRBs, investigators, and HHS funding agencies that may be responsible for review, conduct, or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

HHS regulations for the protection of human subjects ([45 CFR part 46](#)) contain five specific requirements relevant to the review and reporting of unanticipated problems and adverse events:

1. Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)).

2. For research covered by an assurance approved for federalwide use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.
3. In order to approve research conducted or supported by HHS, the IRB must determine, among other things, that:
 - (a) 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 subject for diagnostic or treatment purposes (45 CFR 46.111(a)(1)).
 - (b) Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).
 - (c) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)).
4. An IRB must conduct continuing review of research conducted or supported by HHS at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research (45 CFR 46.109(e)).
5. An IRB must have authority to suspend or terminate approval of research conducted or supported by HHS that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reasons for the IRB's action and must be reported promptly to the investigator, appropriate institutional officials, and any supporting department or agency head (45 CFR 46.113).

Guidance:

I. What are unanticipated problems?

The phrase “unanticipated problems involving risks to subjects or others” is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

1. 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. 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. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks; and
- provision of additional information about newly recognized risks to previously enrolled subjects.

As discussed in the sections II and III below, only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs. See the end of this section for examples of unanticipated problems that do

not involve adverse events but must be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

II. What are adverse events?

The HHS regulations at 45 CFR part 46 do not define or use the term adverse event, nor is there a common definition of this term across government and non-government entities. In this guidance document, the term adverse event in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

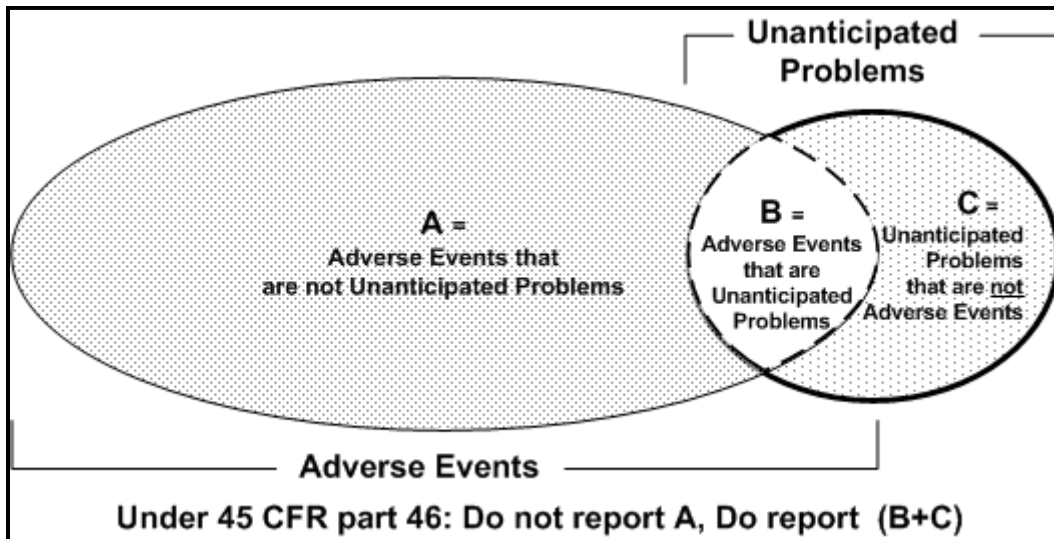
In the context of multicenter clinical trials, adverse events can be characterized as either *internal adverse events* or *external adverse events*. From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

In the case of an internal adverse event at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of external adverse events, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

III. How do you determine which adverse events are unanticipated problems?

In OHRP's experience, most IRB members, investigators, and institutional officials understand the scope and meaning of the term adverse event in the research context, but lack a clear understanding of OHRP's expectations for what, when, and to whom adverse events need to be reported as unanticipated problems, given the requirements of the HHS regulations at 45 CFR part 46.

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



The diagram illustrates three key points:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

The key question regarding a particular adverse event is whether it meets the three criteria described in Section I and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to all three questions is yes, then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). The next three sub-sections discuss the assessment of these three questions.

A. Assessing whether an adverse event is unexpected

In this guidance document, OHRP defines *unexpected adverse event* as follows:

Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

(Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

Examples of *unexpected* adverse events under this definition include the following:

- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information did not identify liver disease as a potential adverse event;
- Hodgkin's disease (HD) occurring in a subject without predisposing risk factors for HD would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information only referred to acute myelogenous leukemia as a potential adverse event; and
- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected greater severity) if the protocol-related documents and other relevant sources of information only referred to elevated hepatic enzymes or hepatitis as potential adverse events related to the procedures involved in the research.

In comparison, prolonged severe neutropenia and opportunistic infections occurring in subjects administered an experimental chemotherapy regimen as part of an oncology clinical trial would be examples of expected adverse events if the protocol-related documents described prolonged severe neutropenia and opportunistic infections as common risks for all subjects.

OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected. OHRP notes that for many studies, determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research.

In OHRP's experience the vast majority of adverse events occurring in the context of research are expected in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of subjects' underlying diseases, disorders, and conditions; and (3) subjects' predisposing risk factor profiles for the adverse events. Thus, most individual adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5) (see examples at the end of this section).

B. Assessing whether an adverse event is related or possibly related to participation in research

Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;
2. an underlying disease, disorder, or condition of the subject; or
3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

For example, for subjects with cancer participating in oncology clinical trials testing chemotherapy drugs, neutropenia and anemia are common adverse events related to participation in the research. Likewise, if a subject with cancer and diabetes mellitus participates in an oncology clinical trial testing an investigational chemotherapy agent and experiences a severe hypoglycemia reaction that is determined to be caused by an interaction between the subject's diabetes medication and the investigational chemotherapy agent, such a hypoglycemic reaction would be another example of an adverse event related to participation in the research.

In contrast, for subjects with cancer enrolled in a non-interventional, observational research registry study designed to collect longitudinal morbidity and mortality outcome data on the subjects, the death of a subject from progression of the cancer would be an adverse event that is related to the subject's underlying disease and is unrelated to participation in the research. Finally, the death of a subject participating in the same cancer research registry study from being struck by a car while crossing the street would be an adverse event that is unrelated to both participation in the research and the subject's underlying disease.

Determinations about the relatedness of adverse events to participation in research commonly result in probability statements that fall along a continuum between definitely related to the

research and definitely unrelated to participation in the research. OHRP considers possibly related to participation in the research to be an important threshold for determining whether a particular adverse event represents an unanticipated problem. In this guidance document, OHRP defines possibly related as follows:

There is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

OHRP recognizes that it may be difficult to determine whether a particular adverse event is related or possibly related to participation in the research.

Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5) (see examples at the end of this section).

C. Assessing whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

In this guidance document, OHRP defines *serious adverse event* as any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

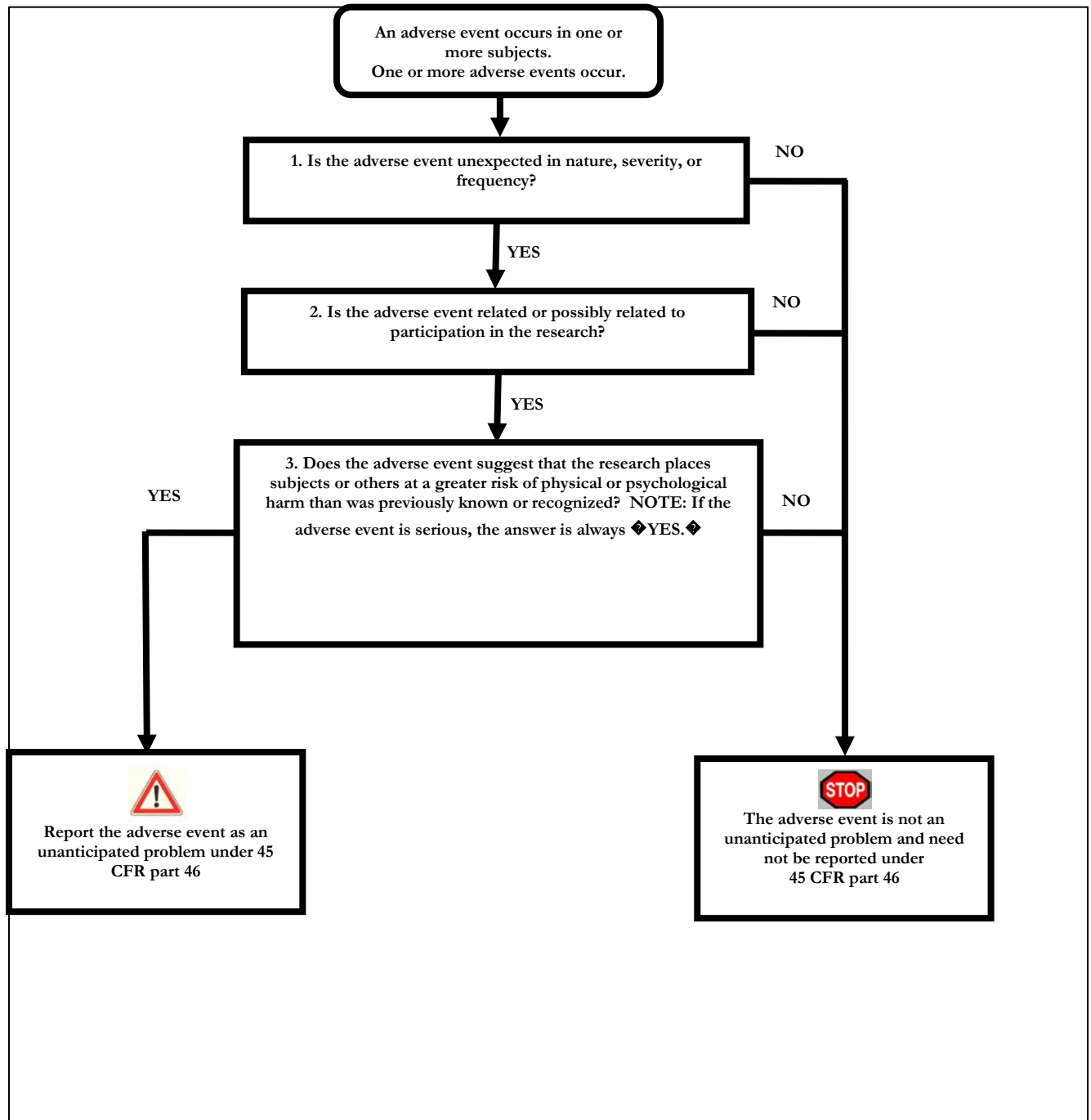
OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects (see examples at the end of this section).

Furthermore, OHRP notes that IRBs have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to subjects (45 CFR 46.113). In order for IRBs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, related or possibly related to participation in the research, and serious (45 CFR 46.103(b)(5)).

However, other adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others (see examples at the end of this section).

The flow chart on the next page provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR part 46.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



IV. What are other important considerations regarding the reviewing and reporting of unanticipated problems and adverse events?

A. Reporting of internal adverse events by investigators to IRBs

For an internal adverse event, a local investigator typically becomes aware of the event directly from the subject, another collaborating local investigator, or the subject's healthcare provider.

Upon becoming aware of an internal adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the guidelines described in section III above. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).

Regardless of whether the internal adverse event is determined to be an unanticipated problem, the investigator also must ensure that the adverse event is reported to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).

B. Reporting of external adverse events by investigators to IRBs

Investigators and IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials. These external adverse event reports frequently represent the majority of adverse event reports submitted by investigators to IRBs. OHRP notes that reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse

events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Typically, such reports to the IRBs are submitted by investigators. OHRP recommends that any distributed reports include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

1. unexpected;
2. related or possibly related to participation in the research; and
3. serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems under HHS regulations at 45 CFR 46.103(b)(5). OHRP expects that individual external adverse events rarely will meet these criteria for an unanticipated problem.

C. Reporting of other unanticipated problems (not related to adverse events) by investigators to IRBs

Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event; see the end of this section for examples) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described in Section I. If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).

D. Content of reports of unanticipated problems submitted to IRBs

OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

1. appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
2. a detailed description of the adverse event, incident, experience, or outcome;
3. an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and
4. a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

E. Changes to a multicenter research protocol that are proposed by an investigator at one institution in response to an unanticipated problem

For multicenter research protocols, if a local investigator at one institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an unanticipated problem, the investigator should consult with the study sponsor or coordinating center regarding the proposed changes because changes at one site could have significant implications for the entire research study.

F. IRB review and further reporting of unanticipated problems

Once reported to the IRB, further review and reporting of any unanticipated problems must proceed in accordance with the institution's written procedures for reporting unanticipated problems, as required by HHS regulations at 45 CFR 46.105(b). The HHS regulations at 45 CFR part 46 do not specify requirements for how such unanticipated problems are reviewed by the IRB. Therefore, IRBs are free to implement a wide range of procedures for reviewing unanticipated problems, including review by the IRB chairperson or another IRB member, a subcommittee of the IRB, or the convened IRB, among others. When reviewing a report of an unanticipated problem, the IRB should consider whether the affected research protocol still satisfies the requirements for IRB approval under HHS regulations at 45 CFR 46.111. In particular, the IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.

When reviewing a particular incident, experience, or outcome reported as an unanticipated problem by the investigator, the IRB may determine that the incident, experience, or outcome does not meet all three criteria for an unanticipated problem. In such cases, further reporting to appropriate institutional officials, the department or agency head (or designee), and OHRP would not be required under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

The IRB has authority, under HHS regulations at 45 CFR 46.109(a), to require, as a condition of continued approval by the IRB, submission of more detailed information by the investigator(s), the sponsor, the study coordinating center, or DSMB/DMC about any adverse event or unanticipated problem occurring in a research protocol.

Any proposed changes to a research study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to subjects. If the changes are more than minor, the changes must be reviewed and approved by the convened IRB (45 CFR 46.103(b)(4) and 46.110(a)). OHRP recommends that for multicenter research protocols, if the IRB proposes changes to the protocol or informed consent documents/process in addition to those proposed by the study sponsor, coordinating center, or local investigator, the IRB should request in writing that the local investigator discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the IRB.

Institutions must have written procedures for reporting unanticipated problems to appropriate institutional officials (45 CFR 46.103(b)(5)). The regulations do not specify who the appropriate institutional officials are. Institutions may develop written procedures that specify different institutional officials as being appropriate for different types of unanticipated problems. For example, an institution could develop written procedures designating the IRB chairperson and members as the only appropriate institutional officials to whom external adverse events that are unanticipated problems are to be reported, and designating the Vice President for Research as an additional appropriate institutional official to whom internal adverse events that are unanticipated problems are to be reported by the IRB chairperson.

G. Reporting unanticipated problems to OHRP and supporting agency heads (or designees)

Unanticipated problems occurring in research covered by an OHRP-approved assurance also must be reported by the institution to the supporting HHS agency head (or designee) and OHRP (45 CFR 46.103(a)). Typically, the IRB chairperson or administrator, or another appropriate institutional official identified under the institution's written IRB procedures, is responsible for reporting unanticipated problems to the supporting HHS agency head (or designee) and OHRP. For further information on reporting to OHRP, see the Guidance on Reporting Incidents to OHRP at http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html.

For multicenter research projects, only the institution at which the subject(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.103(b)(5)). Alternatively, the central monitoring entity may be designated to submit reports of unanticipated problems to the supporting agency head (or designee) and OHRP.

V. What is the appropriate time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP?

The HHS regulations at 46.103(b)(5) require written procedures for ensuring prompt reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

The regulations do not define prompt. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, OHRP recommends the following guidelines in order to satisfy the requirement for prompt reporting:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
3. All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

OHRP notes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, appropriate institutional officials, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

VI. What should the IRB consider at the time of initial review with respect to adverse events?

Before research is approved and the first subject enrolled, the investigator(s) and the IRB should give appropriate consideration to the spectrum of adverse events that might occur in subjects. In particular, in order to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111(a)(1), (2), and (6), the IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may be caused by the procedures involved in the research. The investigator also should describe how the risks of the research will be minimized.

In addition, depending upon the risks of the research and the likelihood that the research could involve risks to subjects that are unforeseeable, the IRB must ensure, if appropriate, that the research includes adequate provisions for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)). Such provisions typically would include monitoring, among other things, adverse events and unanticipated problems that may occur in subjects enrolled in the research. The HHS regulations at 45 CFR part 46 do not require that the IRB conduct

such monitoring, and OHRP believes that, in general, the IRB is not the appropriate entity to monitor research.

OHRP notes that adequate monitoring provisions for research, if deemed appropriate by the IRB, might include one or more of the following elements, among others:

1. The type of data or events that are to be captured under the monitoring provisions.
2. The entity responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB/DMC, and/or some other entity). (OHRP notes that the IRB has authority to observe or have a third party observe the research (45 CFR 46.109(e).)
3. The time frames for reporting adverse events and unanticipated problems to the monitoring entity.
4. The frequency of assessments of data or events captured by the monitoring provisions.
5. Definition of specific triggers or stopping rules that will dictate when some action is required.
6. As appropriate, procedures for communicating to the IRB(s), the study sponsor, the investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.

The monitoring provisions should be tailored to the expected risks of the research; the type of subject population being studied; and the nature, size (in terms of projected subject enrollment and the number of institutions enrolling subjects), and complexity of the research protocol.

For example, for a multicenter clinical trial involving a high level of risk to subjects, frequent monitoring by a DSMB/DMC may be appropriate, whereas for research involving no more than minimal risk to subjects, it may be appropriate to not include any monitoring provisions.

VII. What should the IRB consider at the time of continuing review with respect to unanticipated problems and adverse events?

For non-exempt research conducted or supported by HHS, the IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)). At the time of continuing review, the IRB should ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 continue to be satisfied. In particular, the IRB needs to determine whether any new information has emerged either from the research itself or from other sources that could alter the IRB's previous determinations, particularly with respect to risk to subjects. Information regarding any unanticipated problems

that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review.

It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

OHRP recommends that, among other things, a summary of any unanticipated problems and available information regarding adverse events and any recent literature that may be relevant to the research be included in continuing review reports submitted to the IRB by investigators. OHRP notes that the amount of detail provided in such a summary will vary depending on the type of research being conducted. In many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

OHRP recognizes that local investigators participating in multicenter clinical trials usually are unable to prepare a meaningful summary of adverse events for their IRBs because study-wide information regarding adverse events is not readily available to them. In such circumstances, when the clinical trial is subject to oversight by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC), OHRP recommends that at the time of continuing review local investigators submit to their IRBs a current report from the monitoring entity. OHRP further recommends that such reports include the following:

1. a statement indicating what information (e.g., study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;
2. the date of the review; and
3. the monitoring entity's assessment of the information reviewed.

For additional details about OHRP's guidance on continuing review, see <http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm>.

VIII. What should written IRB procedures include with respect to reporting unanticipated problems?

Written IRB procedures should provide a step-by-step description with key operational details for complying with the reporting requirements described in HHS regulations at 45 CFR 46.103(b)(5). Important operational details for the required reporting procedures should include:

1. The type of information that is to be included in reports of unanticipated problems.
2. A description of which office(s) or individual(s) is responsible for promptly reporting unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency heads (or designees), and OHRP.
3. A description of the required time frame for accomplishing the reporting requirements for unanticipated problems.
4. The range of the IRB's possible actions in response to reports of unanticipated problems.

OHRP notes that many institutions have written IRB procedures for reporting adverse events, but do not address specifically the reporting requirements for unanticipated problems. Such institutions should expand their written IRB procedures to include reporting requirements for unanticipated problems.

Glossary of Key Terms

Adverse event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Unanticipated problem involving risks to subjects or others: Any incident, experience, or outcome that meets all of the following criteria:

1. 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. related or possibly related to a subject's participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

(Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

- An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.
- As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.
- Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an unanticipated problem that must be reported because the incident was (a) unexpected; (b) related to participation in the

research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these examples, the unanticipated problems warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

- A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is not an unanticipated problem because the occurrence of severe infections and death in terms of nature, severity, and frequency was expected.
- A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and

withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers in terms of nature, severity, and frequency was expected.

- A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention. This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.
- An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions in terms of nature, severity, and frequency was expected.
- A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research. This example is not an unanticipated problem because the subject's pulmonary embolus and death were attributed to causes other than the research interventions.

- An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This example is not an unanticipated problem because the death of the subject is not related to participation in the research, but is most likely related to the infant's underlying medical condition.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research. In addition, the assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event.

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

- A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo- controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the subject's acute renal failure was (a) unexpected in nature, (b) related to participation in the research, and (c) serious.
- A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include

anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

- The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was (a) unexpected in severity; (b) possibly related to participation in the research; and (c) serious.
- Subjects with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and informed consent document. After the first 20 subjects are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the investigators. This is an example of an unanticipated problem that must be reported because (a) the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency; (b) these events were related to participation in the research; and (c) these events were serious.

- Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.
- A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In all of these examples, the adverse events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes

that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research.

7.5 Protocol Exceptions (Investigator-Initiated Studies)

This section was added to the OPHS-IRB manual on 1/11/11 to address reporting requirements for protocol exceptions for investigator-initiated (non-clinical trial) studies.

Note: This section is applicable to investigator-initiated (non-clinical trial) studies only.

A protocol exception is a planned “one-time” change to the research protocol. It differs from a protocol modification because it is a temporary deviation from the IRB approved protocol that involves a single subject or, in some cases, a small group of subjects. Similar to a protocol modification, IRB approval of a protocol exception must occur prior to its implementation. Investigators who fail to submit a protocol exception to the OPHS/IRB for review and approval are considered to be in non-compliance with the federal regulations and University policy, because they have modified the protocol without prior IRB review and approval. Thus, the “protocol exception” allows for special circumstances where the protocol can be modified on a single subject case-by-case basis.

Examples of protocol exceptions include:

- Enrolling a subject who does not meet the inclusion criteria
- Bypassing an essential study procedure for a particular subject
- Inviting a subject back for another study visit to repeat some of the study tests or questionnaires
- Adding a “one-time” procedure essential for subject safety within the designs of the protocol

Before initiating the change, the PI is responsible for submitting to OPHS and the IRB a *signed (by the principal investigator) memorandum* clearly describing and justifying the need for a protocol exception along with any related risk/benefit information. OPHS will review the request, contact the investigator if necessary for additional information, and consult with the OPHS Director to determine if the request for exception requires review by the Full Board or may be reviewed by the IRB Chair (or IRB member designated by the IRB Chair).

During review, the IRB Chair (or convened Board if necessary) will evaluate the impact of the protocol exception on the scientific soundness of the research, potential benefits, and the rights, safety, and welfare of the subjects. IRB determination will be communicated to the investigator in writing, and only those protocol exceptions that have been IRB approved should be implemented.

Note that if a protocol exception is not granted by the IRB Chair, the principal investigator may request, in writing, a reconsideration of the exception by the convened IRB at its next regular meeting, following the documentation procedure described above. Note that protocol exceptions should be considered rare events. Any change to the protocol involving more than one subject on a given item or concern, should be submitted and reviewed as a protocol modification (amendment) for the entire project.

7.6 Project Closure

The number of this section changed from 7.5 to 7.6 on 1/11/11 as a result of the new section on Protocol Exceptions (see above).

A final continuing review application (Progress Report) is required by the IRB at the completion or termination of the study. Using the same form as for continuing review, the PI includes the appropriate information as indicated on the form.

When a study ends, is closed, or canceled for any reason, a final progress report must be submitted to the IRB through OPHS, by completing a continuing review/Progress Report. This report may serve as notification to the IRB, that further IRB continuing review of the study is no longer needed.

For studies involving industry-sponsored clinical trials (drugs, devices, biologics) the principal investigator needs to coordinate this close-out with both the OPHS and the Office of Clinical Trials to assure compliance with federal regulations as well as contractual terms.

If no subjects have been enrolled in a study for a period of two or more years, the OPHS on behalf of the IRB may require the investigator to close the study unless there are extenuating circumstances for keeping a study open (e.g. the study is about a rare condition).

A study that is closed to enrolling new subjects may still be collecting follow-up data on subjects. In this case, the project must remain open (no Final Report) and requires continuing review until the collection of all follow-up data has ceased. Once a final progress report (continuing review application) is submitted to the IRB, data collection about any of the subjects must stop. Studies that are closed to enrollment but open for “data collection only” are subject to continuing review.

When submitting a final report, the investigator should submit 1 copy (original with signature) of the progress report form and 1 copy of the IRB approved consent form (with the stamp). Final Reports/Close outs do not require updated conflict of interest forms.

Record Keeping Requirements for Investigators

Every PI is required by UNTHSC and federal regulations to maintain records of all correspondence relating to the use of human subjects in research. Copies of the IRB application, correspondence from the IRB, notices of approval, approved consent and recruitment documents, and signed Informed Consent Forms must be maintained in the

investigator's records. All records of human subject research are subject to inspection by federal authorities and the UNTHSC Office for Protection of Human Subjects (OPHS) and the IRB. Copies of all research records must be kept for **three (3) years** after the close of the study (six years if the study involves protected health information or PHI) unless otherwise approved. (Also refer to International Conference on Harmonization guidelines, Section 8.8).

a. FDA RECORDKEEPING REQUIREMENTS FOR A STUDY INVOLVING AN INVESTIGATIONAL DRUG UNDER AN IND (21 CFR 312.62): if a study involves the use of an investigational drug under an IND, Principal Investigators must retain study records and documents until at least the later of the following dates:

1. 2-years following the date a marketing application is approved for the drug for the indication for which it was being investigated; or,
2. 2-years after the investigation is discontinued and the FDA is notified if no marketing application is to be filed or, if the application is not approved for such indication.

b. FDA RECORD-KEEPING REQUIREMENTS FOR A STUDY INVOLVING AN INVESTIGATIONAL DEVICE UNDER AN IDE (21 CFR 812.140): if a study involves an investigational device under an IDE, principal investigators must retain study records and documents until at least the later of the following dates:

1. 2-years following the date on which the investigation is terminated or completed; or
2. 2-years following the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol; or

NOTE – The FDA two-year requirements may occur during the applicable retention period required by the University and other regulations or it may occur afterward and be additional to that period.

HIPAA RECORD-KEEPING REQUIREMENTS - if a study involves the collection of identifiable health information, Principal Investigators must retain study records and documents for six (6) years following study closure. This applies to all studies regardless of funding source if it involves collection of identifiable health information.

Records must be retained longer than the times specified in the above policies if other requirements apply such as may be forthcoming from sponsors in executed contracts or extramural funding agencies.

7.7 Publishing when Data Is Collected for Non-Research Purposes

If data collected for non-research purposes become “research data” (by contributing to generalizable knowledge through publication, change in intent, or the activity is mixed human subjects research/non-human subjects research), the IRB must review and approve the research, prior to the accessing of the data for research purposes.

The implications of engaging in activities that qualify as research subject to IRB review without obtaining such review are significant. Results from such studies may not be published or presented unless IRB approval had been obtained prior to collecting the data. To do so is in violation of UNTHSC policy. It is also against University policy to use such data to satisfy thesis or dissertation requirements. The IRB does not have the authority to grant retroactive approval should a research study be initiated without prior IRB review and approval. Further, federal regulations do not allow an IRB to grant retroactive approval for a research project involving human subjects.

Chapter 8: Investigator's Role and Responsibilities

CHAPTER CONTENTS

- Definition and Role of Principal Investigator (PI)
- Educational Requirements
- Professional Qualifications of Principal Investigators
- UNTHSC Investigators who Perform Research Outside of UNTHSC
- Investigator Conflict of Interest
- Faculty Advisors Assurance for Student Investigators
- Student Investigator's/House Officer's Application Signature
- Failure to Submit a Project for IRB Review
- Scientific/Research Misconduct
- Transfer of Principal Investigator Status

Overview

This chapter defines the role of a Principal Investigator, co-investigator, and student investigator. It identifies the specific responsibilities, qualifications, and interactions an investigator has when conducting research

8.1 Definition and Role of Principal Investigator (PI)

This section was modified on 2/23/11 to provide a “more specific” definition of who can serve as PI at the UNT Health Science Center.

“The Principal Investigator is responsible for everything.”

The term Principal Investigator (PI) implies specific responsibilities and interactions with a research project. The PI is responsible for the scientific, technical, and administrative aspects of the research project even when certain responsibilities have been delegated to their staff, students or co-investigators. The PI initiates the research proposal, defines the scope of the work, controls the conduct of research, and directly supervises other faculty, staff and students involved in the research. The PI specifies and participates in the selection of supplies, equipment, and subcontractors. The PI certifies the percentage of effort for other faculty and staff working on the project, certifies the accuracy of other charges, notifies and communicates with sponsor personnel and collaborating organizations as needed, and manages the orderly execution and close out of the project.

The PI is responsible for securing the necessary administrative and research compliance committee approvals prior to commencing sponsored research. For example, all sponsored proposals submitted to the UNTHSC IRB that involve industry-sponsored activities (i.e. clinical trials) must first be processed through the Office for Clinical Trials (OCT) and/or any Department/Institute at UNTHSC that requires *a priori* review and approval before submission to the IRB.

The PI is also responsible for ensuring that the appropriate research compliance committee (e.g., IRB, Institutional Animal Care and Use Committee, etc.) has reviewed and approved a sponsored project's protocol in accordance with those committees' principles and procedures. Studies submitted to the IRB may require school or department approvals as determined by the particular school or department.

If the research project involves a drug, device, or biologic the PI is also responsible for full compliance with all relevant and appropriate FDA regulations (21 CFR) as well as contractual obligations toward the sponsor.

PIs are required to submit an application for IRB review and approval **PRIOR** to initiating a research project. All IRB applications must be submitted through the Office for the Protection of Human Subjects (OPHS).

Who May Serve as Principal Investigator Conducting Human Subject Research

To be consistent with other UNTHSC policies and procedures, the following applies to persons planning or otherwise engaged in the conduct of human subject research:

In general, the term “Principal Investigator” shall encompass the terms Principal Investigator, Project Director, Program Director and the like, and shall mean a single individual who shall have the full and final responsibility for the conduct of the protocol.

Persons eligible to be Principal Investigators shall be:

- Full-time and/or part-time regular and/or non-regular faculty of UNTHSC
- Full-time or part-time non-faculty employees of UNTHSC who are NOT students at UNTHSC. Note that students shall not serve in the capacity or role of Principal Investigator (except as noted below)
- Other individuals without faculty or employee status may serve as Principal Investigators with written approval from the Vice President for Research. Examples of individuals who will need the approval of the Vice President for Research to be a principal investigator are:
 - Graduate students
 - Visiting professors (any rank)
 - Post-doctoral positions including medical residents
 - Adjunct Professors at any rank
 - Anyone not in a permanent UNTHSC employee position

Procedures and Responsibilities:

An individual who wishes to obtain approval as a Principal Investigator from the Vice President for Research should follow these procedures:

1. Submit a written request to the Vice President for Research which provides the rationale for the individual to serve as Principal Investigator. This request must be submitted to the Office of Research for consideration by the Vice President for Research.
2. If such status is granted, the Vice President for Research will then notify the Director, Office for the Protection of Human Subjects (OPHS) of the status of this newly designated Principal Investigator.

8.2 Educational Requirements

This section was modified on 2/4/10. The requirements for the CITI Refresher course were changed to every 3 years. The “Regulation of Human Subject Research” course number was updated, and it will now satisfy the educational training requirements for 6 years.

This section was modified on 1/11/11 regarding accepting NIH training as a substitute for CITI training.

This section was modified on 1/31/11 to clarify that the Good Clinical Practice Course and the Responsible Conduct of Research Courses are not substitutes for the Basic CITI Courses in the Protection of Human Subjects.

This section was modified on 2/14/11 to clarify Waiver of CITI Training Requirement for non-UNTHSC personnel.

This section was modified on 6/10/11 to add an Important Note about human subject research education compliance and documentation.

In accordance with federal regulations, it is necessary for all individuals identified as “key personnel” on a research project involving human research subjects to complete required educational training on the protection of human research subjects.

When submitting a protocol for IRB review (both new and continuing review), the Principal Investigator must include written verification that each of the key personnel on that project has successfully completed the appropriate educational tutorial/program regarding human research protection. As designated by the UNTHSC Office for the Protection of Human Subjects (OPHS), this educational requirement is met through the CITI (Collaborative IRB Training Initiative) Course in the Protection of Human Subjects, with links located on the UNTHSC OPHS-IRB web site at <http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm>. This is the basic standard training requirement for all faculty, staff, and students engaged in research involving human subjects. Completion of the basic CITI course may take a total of up to 4 hours to complete, but can be done in small time and modular increments. Key personnel can choose to complete a Basic Course that has either a Biomedical Focus or a Social and Behavioral Focus dependent upon the type of research that they are conducting. All research personnel who are actively involved with the project (principal investigator, co-investigators, study physician, research assistants, coordinators, etc.) and anyone who will be interacting with human subjects from a research perspective are considered “key personnel” and must complete this training. When in doubt about your own, or a staff person’s involvement in a project, call OPHS for special interpretation. However, the human research protection program at UNTHSC is a campus-wide endeavor. CITI training is a good thing for anyone, and we encourage staff members who think they may be only marginally involved in a project to go ahead and take the training at their own pace. It’s educational, informative (and free!) and broadens awareness of what human subject research is all about.

Initial CITI training for UNTHSC research faculty staff and students is valid for three (3) years. A Refresher Course for CITI trainees will be required every three (3) years thereafter. This refresher course is primarily a series of updates on changing regulations, findings and case studies that impact human subject researchers. The Refresher Course takes about 1 hour to complete.

Note that the Refresher Course is not a substitute for the Basic Course for first time CITI trainees. Additionally, completion of the Good Clinical Practice (GCP) Course or any of the Responsible Conduct of Research (RCR) Courses is not a substitute for the Basic Course or the Refresher Course. While completion of the GCP and RCR courses may be required by other departments or units at the UNT Health Science Center, these courses are not a requirement of the OPHS/IRB for human subjects research.

Alternatively, the educational training requirement for UNTHSC can be met through any one of the following:

- Documentation of current active certification as either a Clinical Research Coordinator (CRC), Clinical Trial Investigator (CTI), or Clinical Principal Investigator (CPI) as designated and verified by the Association of Clinical Research Professionals (ACRP). Persons desiring to use this alternative to CITI training must present a copy of a valid and current certification.
- Documentation of current active certification as a Certified IRB Professional (CIP) as designated and verified by Public Responsibility in Medicine and Research (PRIM&R) Council for Certification of IRB Professionals (CCIP). Persons desiring to use this alternative to CITI training must present a copy of a valid and current certification as documented by that organization.
- Successful completion (passing grade) of the course BMSC 5203 “Regulation of Human Subject Research” offered by UNTHSC (good for 6 years only).
- Previous completion of CITI training at another institution. Note that CITI certification applies to a given individual across all institutions.
- NIH training in the “Protection of Human Research Participants” (<http://phrp.nihtraining.com/users/login.php>) is acceptable as a substitute for CITI training only if that NIH training was completed after April 30, 2008. However, for this training to be accepted at UNTHSC, the trainee must provide the appropriate NIH Protection of Human Research Participants certificate of completion to OPHS prior to involvement in any project involving human subjects. Initial NIH training will be valid for 3 years from the date that it was completed. Re-training will be required every 3 years thereafter.

Note that all other non-CITI on-line training by other universities, programs or organizations do not meet this educational requirement. Although such programs can provide useful information, they do not qualify as a substitute for CITI educational training program under this policy.

Offsite investigators and study personnel (such as medical residents and clinicians in private practice) may substitute CITI training with NIH training as long as the NIH training was completed after April 30, 2008.

Waiver of CITI Training Requirement for non-UNTHSC personnel

In special circumstances, the UNTHSC human research subject CITI training requirement may be waived by the Director, OPHS for certain non-UNTHSC key personnel if, in the opinion of the OPHS Director, such a CITI certificate waiver does not constitute a risk to human subjects and would be impractical. Such cases would involve Case Study or Chart Review projects research projects that meet the 45 CFR 46 criteria for EXEMPT (minimal

risk and not requiring IRB review) AND where non-UNTHSC key personnel are formally affiliated with another institution (such a hospital or clinical practice serving as a student or residency site). Other waivers may be granted by the Director, OPHS on a case-by-case basis.

Important Note:

Human subject research education and training is a federal, as well as University, requirement of all persons engaged in human subject research. The goal of CITI on-line training is to provide such education in a convenient efficient manner, rather than with in-class lectures and tests. Proper compliance and documentation for this requirement is essential. Efforts by learners and others to circumvent the spirit as well as the practical importance of this educational requirement are inappropriate and counter-productive. Anyone taking CITI training on behalf of another person or otherwise circumventing this requirement (use of multiple screens, taking the quizzes without reading and understanding the preceding content, use of alternate user ids, etc.) is engaged in academic and research misconduct and falsification of data. Such inappropriate use of the CITI training program will be referred to appropriate university officials for action. Also note that such misconduct on federally-funded research projects constitutes a violation of federal policies and procedures and will be reported to the appropriate university compliance officers who may then report such events to federal agency officials for further investigation.

8.3 Professional Qualifications of PIs

For projects that are more than minimal risk (i.e. Full Board), the UNTHSC IRB requires PIs to provide a copy of their curriculum vitae, and as necessary/requested, additional supporting information to document that the investigator is qualified to conduct the research activity.

For studies requiring involvement of a physician (MD, DO, etc.) a copy of the current state medical license verifying authorization to practice medicine in the state of Texas is also required with protocol submission.

All UNTHSC investigators (including students) are required to take human subjects education Collaborative IRB Training Initiative (CITI) as described above.

8.4 UNTHSC Investigators Who Perform Research Outside of UNTHSC

UNTHSC investigators may conduct research at other sites. Such research may be required to be reviewed and approved by that “off-site local IRB” or equivalent research review ethics board, in addition to approval from a UNTHSC IRB. When applicable, investigators should

submit a copy of the permission or approval letter to conduct the research at a non-UNTHSC site to OPHS.

Recall that **all** research involving UNTHSC personnel must have prior review and approval by the UNTHSC IRB. Thus, the PI must obtain IRB approval at UNTHSC before seeking IRB review elsewhere. And in some situations, this “UNTHSC review first” approach can facilitate IRB review at other institutions.

8.5 Investigator Conflict of Interest

Section updated (page 132) on 10/19/10 (clarification on reporting requirements for changes in conflict of interest disclosure status).

Background

Public trust in the research enterprise and the legitimacy of its powerful role in society require a constant amenability to public scrutiny. Consequently, it is necessary at all times to assure the continued confidence of the public in the judgment of scholars and clinicians and in the dedication of academic research institutions to the integrity of the research enterprise. The strength of this assurance is based on the assumption that scholars are honest and conduct their research with the highest standards and integrity.

This policy is intended to serve subjects of human research. This policy is not intended to eliminate all situations of conflict of interest, but rather to enable individuals to recognize situations that may be subject to questions or concerns and thus resolve them so as to avoid conflicts of interest or the appearance of conflicts of interest. Therefore an integral part of the policy and procedures is disclosure whereby individuals regularly review their professional activities.

Conflict of Interest policy considerations apply to all researchers at UNTHSC. The term “conflict of interest” in this policy refers to situations in which financial, or other personal considerations – compromise, or have the appearance of directly and significantly compromising – an individual’s professional judgments in proposing, conducting or reporting research. The bias caused by such conflicts may affect collection, analysis, and interpretation of data, hiring of staff, procurement of materials, sharing of results, choice of protocol, involvement of human subjects, and the use of statistical methods.

All UNTHSC key personnel are required to disclose any conflict of interest they might have at the time of the initial IRB Application and again at the time of each continuing review. Additionally, key personnel are required to notify the IRB of any new (or change in) conflict of interests that arise during the course of the study that were not previously reported at the time of the initial IRB application or during the most recent continuing review. A new (updated) Conflict of Interest form (completed and signed) and, if needed, a letter of explanation providing the IRB with additional information to consider must be submitted to the OPHS/IRB within 10 business days of becoming aware of the change in disclosure status. It is expected that the PI will disclose appropriate conflict of

interest information to the IRB in addition to disclosure to their division/department/school. IRB reviewers are then required to evaluate disclosed (or knowingly withheld) conflicts of interest during the protocol review process.

In addition to the IRB, it is important for investigators to disclose any conflict of interest they may have to the subjects who participate in their study. This may be done through a statement in the consent form. OPHS staff can provide additional guidance in this area when necessary.

If the investigator declares, or if it is discovered that the investigator has a conflict of interest with regards to the study, the IRB may defer approval or approve with contingencies. The IRB has the final authority to decide whether the conflicting interest is manageable and to allow the research to proceed.

ALL UNTHSC key personnel (including students) on protocols submitted to the OPHS for IRB review must complete and sign an IRB Conflict of Interest Statement (Expedited and Full Board IRB applications only). A new (updated) Conflict of Interest form (completed and signed) will be required at the time of continuing review for all key personnel listed on the study. A Conflict of Interest form is also required for all new study personnel who are added using the Application for Change in Study Personnel.

Note that this OPHS-IRB requirement is independent of any other Conflict of Interest report or documentation that may be required of another unit of the University (Grants and Contracts, Vice President for Research, etc.).

Also note that this OPHS-IRB conflict of interest disclosure requirement does not involve signatures other than that of each individual person associated with the protocol. For the purposes of protocol review, the IRB does not require a Conflict of Interest co-signature from Department Heads, Deans, or any other University official

Based on the information submitted by the researcher for review, the IRB may determine that:

- no conflict exists, or
- a conflict exists and must be disclosed to the subjects in the informed consent statement, or
- a conflict exists and the researcher must resolve the conflict before the research can be approved.

EXAMPLES OF REPORTABLE AND NON-REPORTABLE ACTIVITIES

1. Non-Reportable Activities

The following are examples of activities and relationships do not need to be reported and do not represent a conflict of interest because they have been generally accepted practices and do not violate fundamental ethical principles:

- Receiving royalties for published scholarly works and other writings not sponsor-paid.
- Accepting honoraria for commissioned papers and occasional lectures, again not sponsor-paid.
- Receiving payment for reasonable travel and lodging expenses related to presentations of scholarly work or to a person's academic endeavor, payments not from sponsors.
- Investing in mutual funds.
- Participating in a University approved Practice Corporation.
- Payments for clinical research to an approved practice corporation or to a department fund for salary or other expenses of conducting clinical trials.

2. Reportable Activities

1. Conducting research in applied and/or clinical research on a technology developed by the investigator or a member of his/her immediate family (e.g. spouse, children, parent, in-laws, and siblings).
2. The financial relationship of an investigator or his/her immediate family member with the sponsor of his/her research (acting as scientific advisor or consultant, or receiving honoraria exceeding \$5,000 annually, or acting as the director or other executive).
3. Conducting applied and/or clinical research on a technology owned by a business in which the investigator or a member of his/her immediate family holds 5% or more of the outstanding stock or stock options.
4. Receiving royalties under institutional royalty-sharing policies from marketing the drug, device or procedures that is the subject of the research.
5. Receiving payments directly from the sponsor, rather than through the University or an approved UNTHSC entity, for recruiting subjects into a research study.

8.6 Faculty Members' Assurance for Student Investigators / Medical Residents (non-faculty)

The faculty advisor certifies that the student investigator/medical resident (non-faculty) is knowledgeable about IRB principles and procedures, and applicable federal regulations governing research with human subjects, and has sufficient training and experience to conduct the study in accordance with the approved protocol and has completed the mandatory human

subjects education program (i.e. CITI) for all investigators, including students. Faculty advisors must ensure that student/resident investigators and all key personnel have completed the Human Subjects and the Health Insurance Portability and Accountability Act (HIPAA) Programs when required.

The faculty member is also responsible for the scientific quality of the student/resident research project submitted to the IRB. When a student and/or resident investigator is listed as a Co-Investigator on the IRB application, a faculty member must be listed as the PI, and agrees that they have reviewed the application, it is ready for IRB submission, and that the faculty advisor assumes complete responsibility for oversight of the student's/resident's research.

8.7 Failure to Submit a Project for IRB Review

There are significant implications for engaging in human subject research activities that are required to undergo IRB review, without obtaining prior IRB review and approval. In order to publish or present study outcomes, UNTHSC policy requires investigators to have obtained IRB approval prior to the initiation of any research activities. If an investigator begins a project not intending to contribute to generalizable knowledge but later finds that the study results could be published or presented, IRB approval must be obtained before publishing or presenting the data. Master's theses and doctoral dissertations often lead to generalizable knowledge and seek publication. In these cases, IRB review is required.

Further, engaging in unapproved drug, device, biologic or intervention research involving human subjects without appropriate IRB and other regulatory approval may expose the investigator to civil and/or criminal sanctions.

The IRB may not approve applications where an investigator circumvents IRB principles and procedures by collecting data as a "non-research" activity, and then subsequently applying for IRB approval to analyze the data as existing data. It is in the investigator's best interest to carefully consider the likelihood of the data being used for future research purposes, and err on the side of caution in seeking IRB approval, prior to commencing the work.

8.8 Foreign Sites

Activities conducted at foreign sites should be carefully evaluated to account for cultural norms, health resource capabilities, and official health policies of the host country. The reviewing IRB must consider any modifications to this policy must be significantly justified by the potential risk/benefit ratio evaluation of the research. The IRB may seek expert advice (e.g. local public health experts) in evaluation of these projects. See Section 9 in Chapter 13 on Specialized Research for additional information about foreign sites.

8.9 Scientific/Research Misconduct

At UNTHSC allegations of research misconduct are reported by the IRB and OPHS to the VP for Research, the Director of the Office for the Protection of Human Subjects (OPHS), and the

General Counsel Office for further action (scientific misconduct is not necessarily under the sole purview of the IRB).

The University of North Texas Health Science Center is committed to maintaining an environment that promotes high ethical standards in the conduct of research without inhibiting productivity or creativity of persons involved in research, regardless of the position or level of responsibility of those involved. The University does not tolerate misconduct in any aspect of research and will deal with misconduct associated with research forthrightly, in accordance with academic due process, and with respect for practices commonly accepted within the scientific community.

If a UNTHSC investigator does not conduct research responsibly, according to federal regulations or University policy, the investigator is subject to both federal and UNTHSC consequences. UNTHSC is committed to fairly and uniformly investigating and reporting all instances of alleged or apparent misconduct involving research by members of the University community, regardless of the funding source. For information on how these issues are handled by the University, refer to the UNTHSC “Policy on Scientific Misconduct.”

Useful Links:

Office of Research Integrity (ORI): http://ori.hhs.gov/documents/FR_Doc_05-9643.shtml

National Science Foundation (NSF):
<http://www.nsf.gov/pubs/2002/oigseptember2002/pdfversions/investigations.pdf>

Public Health Service (PHS):
http://www.access.gpo.gov/nara/cfr/waisidx_00/42cfr50_00.html

Office of Science & Technology Policy (OSTP): <http://www.ostp.gov/>

Federal Definition of “Misconduct” from the Executive Office of the President, Office of Science and Technology Policy (OSTP))

Misconduct is defined as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

Fabrication

Making up data or results and recording or reporting them.

Falsification

Manipulating research materials, equipment, or processes – or changing or omitting data or results – such that the research is not accurately represented in the research record.

Plagiarism

The appropriation of another person's ideas, processes, results, or words without giving appropriate credit. Research misconduct does not include "honest errors" or differences in opinion.

A Finding of Research Misconduct Requires That:

- There be a significant departure from accepted practices of the relevant research community; and
- The misconduct be committed intentionally, or knowingly, or recklessly; and;
- The allegation is proven by a preponderance of evidence.

Note that the University has an agreement with the federal government (Federalwide Assurance) to adhere to federal regulations associated with human subject research. Falsification of any document submitted as part of a research study, whether it is federally funded or not, may constitute an act of fraud against the federal government. Researchers are reminded to be diligent about the accuracy of any document submitted as part of a human subject research project.

8.10 Transfer of Principal Investigator Status

The designated Principal Investigator of record for a specific protocol shall remain so unless that person leaves UNTHSC service, re-assigns the protocol to another person who then becomes Principal Investigator of record, or is otherwise unable to serve in the role and capacity of Principal Investigator (serious illness, death, imprisonment, suspension of protocol).

Planned Transfer:

When a Principal Investigator (PI) of record for a specific protocol knows, in advance, that they will be leaving UNTHSC service, or otherwise unable to continue serving as PI, they should send a letter directly to OPHS indicating:

1. IRB Number
2. Title of Protocol
3. Name of Existing PI (of record)
4. Name of New PI
5. Reason for Transfer of PI status: (optional)

The letter should be signed by at least the departing PI (signature by both persons, prior and new PI preferable) and will be effective as of date of letter unless otherwise specified. Investigators should allow sufficient time and effort to bring the new PI current with the protocol to effectively assume all duties and responsibilities. In any case, the transfer of PI should be documented and OPHS as soon as possible before or after the transition occurs to prevent document management and reporting problems.

Please Note: Protocols will be administratively closed by the IRB when a PI leaves the institution and fails to notify the IRB (or amend the protocol by replacing themselves with a new principal investigator) within 3 months (90 days) of his or her departure.

Unplanned Transfer:

In some situations, Principal Investigator status may be changed without *a priori* or timely notice from the PI of record due to serious illness, death, imprisonment, suspension of protocol, or other administrative procedure. In the absence of the PI's formal transfer, the transition may be accomplished by a signed and dated letter from the Department / Unit head including the following:

1. IRB Number
2. Title of Protocol
3. Name of Existing PI (of record)
4. Name of New PI
5. Reason for Transfer of PI status: (required, with a brief explanation for the transfer)

This letter should also be signed both the Department/Unit Head and the newly designated PI and will be effective as of date of letter unless otherwise specified. As always, Principal Investigators newly assigned to direct a protocol should be prepared to effectively assume all duties and responsibilities associated with the project.

Reporting to Outside Agencies:

Where appropriate and required by sponsors, funding agencies, or other organizations, the OPHS shall notify, in a timely manner, project-relevant appropriate officials and organizations of the change in Principal Investigator status.

8.11 Registering a Clinical Trials (ClinicalTrials.gov)

Background

Public Law 110-85, enacted in September 27, 2007 requires that “applicable trials” be registered on the NIH’s website, “ClinicalTrials.gov”. Under the statute, these trials generally include:

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

For clinical trials, the sponsor of the trial (as defined in 21CFR 50.3) is responsible for complying with the requirement to register the trial. The Principal Investigator (PI) or, if delegated, the Study Coordinator is responsible for corresponding with the sponsor to ensure that the sponsor includes the UNTHSC-FW site location under the Contacts and Locations section of the study-specific tab on “ClinicalTrials.gov”. If the sponsor declines to include the UNTHSC-FW site, the PI or designee will notify the Office of Clinical Trials.

For Investigator-Initiated clinical trials that do not involve FDA regulated drugs, biologics or devices as described above, the trial is not required by law to be listed on ClinicalTrials.gov; however, the investigator nonetheless may wish to register the trial and should do so through the Office for the Protection of Human Subjects (OPHS) at UNTHSC (but only after first having obtained UNTHSC IRB approval for that trial).

Here is a link to US Public Law 110-85: <http://prsinfo.clinicaltrials.gov/fdaaa.html>

Principal Investigator Responsibilities

From a UNTHSC investigator’s point of view, in almost all cases, a research investigation involving a drug, device or biologic requiring registration at ClinicalTrials.gov will have been registered by the sponsor and no further registration action is required by the UNTHSC researcher.

Since all industry sponsored drug, biologic or device studies at UNTHSC must first be processed through the Office of Clinical Trials, and, since the sponsor is the responsible party for registration, a clinical trial principal investigator at UNTHSC would not register that trial.

Thus, individual clinical investigators at UNTHSC do NOT need to register their project(s) at ClinicalTrials.gov.

Registering “clinical trials” that do not meet the requirements of the federal law

Occasionally, some journals and some funding agencies may require that an investigator provide evidence that their research project is listed on a “public registry”, even if that study does not involve a drug, device or biologic subject to FDA regulation.

For example, some research involving physical therapy, osteopathic manipulations or psychological interventions may be considered “clinical research” by journal editors or funding agencies, and thus require that such projects be listed on a public registry.

Note that these special situations for registration are not a requirement of federal law, but a stipulation of that particular journal or funding source. In such cases, the project may be listed at ClinicalTrials.gov but only through submission to OPHS. Since the registration process is somewhat cumbersome and information-intensive, OPHS will assist with this registration service to UNTHSC researchers seeking a public registration of their project, on a case-by-case basis. [Again, recall that only FDA regulated research is legally required to be registered at ClinicalTrials.gov].

To minimize unnecessary paperwork and resource allocations, OPHS requires written documentation from the journal or funding agency that specifically states that the project needs to be registered at ClinicalTrials.gov or some other public research registry.

To inquire about the need to register your clinically-oriented research project, and for any questions about the ClinicalTrials.gov registration process, contact OPHS for details.

Chapter 9: Informed Consent Requirements

CHAPTER CONTENTS

- The Process of Consent and Assent
- General Requirements for Informed Consent
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- Legally Authorized Representative
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- Child Assent Requirements
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Overview

Investigators are required to obtain informed consent as a legal and ethical obligation. This chapter discusses the process of consent, the elements of consent, and legal requirements involved when obtaining informed consent from subjects

9.1 The Process of Consent and Assent

Informed consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. The

procedures used in obtaining informed consent must be designed to educate the subject population in terms they can comprehend. Informed consent language and its content (i.e. explanation of the study's purpose, duration, experimental procedures, alternatives, risks, and benefits) must be written in "lay language" that is understandable to the people being asked to participate. The written presentation of information is used to document the basis for consent in addition to serving as a future reference material for the subject. The amount of information contained in the consent and the manner of presentation is generally related to the complexity and risk involved in the research study. The consent document should be revised when deficiencies are noted or when additional information will improve the consent process. Any changes to the informed consent form must be reviewed and approved by the IRB.

The Office for Protection of Human Subjects (OPHS) website provides a good description of the consent process: <http://www.hsc.unt.edu/sites/ophs-irb/>

While the informed consent process is prospective and takes place prior to any research activity, consent should also be an ongoing educational interaction between the investigator and the research subject continuing throughout the study. If an investigator has a relationship with potential subjects (physician-patient, instructor-student, employer-employee), care should be taken to avoid recruitment methods that may be seen as coercive or unduly influential due to the special relationship between the parties. Except in certain minimal risk studies, the Informed Consent form is typically signed after the investigator verbally explains the purpose and procedures involved in the study. The investigator must answer any questions, and provide relevant information that allows the subject to make a prospective, informed decision. The Informed Consent document must be signed before any study data collection procedures begin. The Informed Consent form itself serves as a written source of information for the subject and documents the fact that the process of consent occurred.

Consent

Consent is a legal and ethical concept. Only legally competent adults can give legally effective informed consent. Minors and those individuals who are not competent to provide consent should be given the opportunity to *assent* to participate in the research project.

Assent

Assent is an affirmative, knowledgeable agreement to participate in a research project. Adequate provisions should be made for soliciting the independent, non-coerced assent from minors/children or cognitively-impaired persons who are capable of a knowledgeable agreement. In general, the IRB recommends that children ages seven and older and most cognitively-impaired adults be given the opportunity to assent. In cases where assent is obtained from a minor or cognitively-impaired subject, permission must also be obtained from an authorized representative. In studies involving children, the legally authorized representative may be:

1. The parent;

2. A court-appointed guardian;
3. The court.

A child cannot consent to be in a research study. However, the authorized representatives listed above can consent for the minor child to participate in a research study. Special attention must be given to state law regarding attaining the age of majority (18 years of age) and situations involving emancipated minor subjects. (Refer to Section 12.1 for more information).

9.2 General Requirements for Informed Consent

Federal regulations specify eight basic elements and six additional elements for informed consent (*45 CFR 46.116 and 21 CFR 50.25*). They are as follows:

Purpose and Procedures of the Study

The informed consent form must include “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 the identification of any procedures which are experimental.” This section should clearly identify the procedures that will be followed during the course of the research activity. The procedures should be presented to the subject in the order of their occurrence and should detail the approximate duration for each activity the subject is expected to complete.

Pilot Studies or Phase I Drug Studies

A subject making an informed decision regarding willingness to undertake the risks of a project is a principal element of the informed consent process. The Informed Consent form should indicate that the study is a “pilot” or “Phase I” study and that the subject is one of the first to participate in the process, treatment or intervention.

Experimental Procedure versus Standard of Care

There are situations where the difference between clinically indicated and experimental interventions must be explained for subjects in the “Procedures” section of the Informed Consent form. These sections should contain a clear statement regarding which procedures are experimental and which procedures are standard of care.

Potential Risks and Discomforts

The informed consent form must include “a description of any reasonably foreseeable risks or discomforts to the subject.”

Disclosure of Risks and Discomforts

The Informed Consent form is required to provide subjects with a clear understanding of any risks or discomforts which are reasonably anticipated during their participation in the research. All foreseeable risks and/or discomforts of participating in a research study should be addressed in the “Risks/Discomforts” section of the consent form.

Risk Assessment

Risks should not be understated or overstated. In some cases it is appropriate to cite statistical probability of risk occurrence, risk prevention measures, reversibility and treatment. Appropriate disclosure of the potential risks associated with an intervention can be particularly difficult in clinical regimens where decisions are based upon available data.

Anticipated Benefits

The Informed Consent form must include “a description of any benefits to the subject or to others which may reasonably be expected from the research.”

Direct Benefits

The Informed Consent form should state whether there are any direct benefits to the subject that may reasonably be expected as a result of participation in the research. Examples of direct benefits to the subject may include treatment of an illness or knowledge of value to the subject (e.g., results of a cardiac stress test, results of an educational test, etc.). The potential benefits to the subject should not be overstated, coercive or guaranteed. If there are no benefits to the subject it should be so stated.

Benefits to Society

In some cases there may be no direct benefit to subject but a possible benefit to society from their participation in the research study. This section is suggested to ensure fair representation of potential benefits to prospective subjects. All research should have some underlying potential benefit to society (e.g., advancement of knowledge, health benefit to others, etc.).

NOTE that subject payment for time and effort may not be listed as a benefit. Thus, this section should not address payment issues as a benefit. Payment will be addressed later in the Informed Consent document.

Alternatives to Participation

The informed consent form must include “a disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.”

Therapeutic Alternatives

In clinical research, all Informed Consent forms are required to indicate any therapeutic alternatives available to the subject in the non-research and/or research context that may be of reasonable benefit to the subject. When appropriate, the relative potential risks/benefits ratio of the therapeutic alternative versus the research should be stated. It is important to remember that an alternative could simply be supportive care or “watchful waiting” only. Medical protocols which are not therapeutic in nature should state: “Since this protocol is not therapeutic in nature, the only alternative to participation is not to participate in this research.” For studies involving alternative therapies, the research alternatives as well as other available treatments should be clearly distinguished and described.

Participation Alternatives

In some research projects (typically non-clinical trials), the Informed Consent form should state any alternatives that may be advantageous to the subjects. For instance, if the subjects are students who will receive academic credit, the Informed Consent form should describe the available alternatives to earn equivalent academic credit.

Confidentiality Statement

The informed consent form must include “a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.”

Personal Identifiable Information

Investigators are required to maintain and protect the privacy and confidentiality of all personally identifiable information of all human subjects participating in research, except as required by law or released with the written permission of the subject. Subjects, including children, have the right to be protected against invasion of their privacy, to expect that their personal dignity will be maintained, and that the confidentiality of their private information will be preserved. The more sensitive the research material, the greater the care required in obtaining, handling, and storing data.

Types of Identifiable Information

Information through which subjects may be identified include their names, student identification numbers, hospital ID numbers, social security numbers, driver’s license numbers, home addresses, photographs, videotapes, and the like. Individuals also may be identified by description, for example, as the personnel manager in a particular company, the sixth grade teacher in a certain school, or the pediatric nurse at a local hospital. If information or data to be collected may be traced back to individual subjects, safeguards (described below) should be provided to ensure confidentiality.

Guidelines for Protecting Confidentiality

- Limit recording of personal information to that which is absolutely essential to the research;
- Store personally identifiable data securely and limit access to the Principal Investigator (PI) and authorized staff;
- Code data as early in the research process as possible, and plan for the ultimate disposition of the code linking the data to individual subjects;
- Do not disclose personally identifiable data to anyone other than the research staff without the written consent of the subjects or their legal representative. (Exceptions may be made in case of emergency need for intervention or as required by regulatory agencies).
- Apply for federal Certificates of Confidentiality in all situations for which certificates are reasonable and available. For more information visit the following link:
http://grants.nih.gov/policy/coc/appl_extramural.htm

Limits to Confidentiality

Depending on the subject matter of the research, there may be limits to the investigator's promise of confidentiality to the subject. An example would be if a subject reveals information about possible child or elder abuse or if the investigator and/or the research staff discover the possibility of abuse. (See Chapter 17 for more information.) OPHS recommends the following text for the Informed Consent form:

“Under Texas law, the privilege of confidentiality does not extend to information about sexual or physical abuse of children or the elderly. If any member of the research staff has or is given such information, they are required to report it to the appropriate authorities. The obligation to report includes alleged or probable abuse as well as known abuse.”

NOTE: If the investigator is a mandatory reporter (as defined by state and federal law) this must be reported to the IRB and to the subject. Any sexual or physical abuse must be reported to the appropriate authorities.

FDA Regulated Research

Consent forms used to enroll subjects in FDA regulated research must contain a statement informing the subjects that the FDA may inspect the research records. Researchers will maintain confidentiality of records identifying the subject, to the extent possible.

Injury Statement

For research involving more than minimal risk, the informed consent form must include 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.

Emergency Care and Compensation for Injury

A statement regarding “Emergency Care and Compensation for Injury” is a required element of the Informed Consent Form for all research that presents more than minimal risk as determined by the IRB [45 CFR 46.116(a)(6)]. “Minimal risk,” as defined by the federal regulations, is “where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” [45 CFR 46.102(i)].

For example, the risk of drawing a small amount of blood from a healthy adult for research purposes is no greater than the risk of doing so as part of a routine physical examination. Investigators should explain in the Informed Consent form whether any compensation/medical treatments are available if injury occurs and, if so, describe the extent and nature of the compensation.

For studies involving greater than minimal risk, an “injury clause” must be included in the Informed Consent Form. See the informed consent guide for specific template language. UNTHSC does not have funds set aside for any medical care resulting from study-related injuries. In addition, UNTHSC does not have funds set aside to compensate subjects for study-related injuries. Subjects participating in studies at UNTHSC facilities will be given medical care for study-related injuries if needed, however the subjects must pay for the care. If the sponsor has agreed to provide compensation in case of injury to research subjects, the extent/limitations of the compensation should be stated clearly in the informed consent form. The following statement should be considered and agreed to by the sponsor:

“If you are injured as a direct result of these research procedures, you will receive.... (explain the compensation for medical treatments that are available if injury occurs, and describe the extent and nature of the compensation or payment).”

Contact Information

The Informed Consent must include “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.” Usually this is the PI and the IRB Chair.

Identification of Investigators

All Informed Consent forms must include a section explaining who can be contacted for answers to questions about the research, such as the results, and whom to contact in the event of a research related injury [45 CFR 46.116(a)(7)]. The “Identification of Investigators” section should clearly identify the members of the research staff who may be contacted and a contact telephone number that can be used **(24 hours a day, 7 days a week for greater than minimal risk studies)**.

Note that this contact information should be useful and direct, and not a standard “phone tree” or voice-messaging system in which subjects cannot directly contact the investigator or designee at any time, especially after regular business hours.

Participation and Withdrawal

The informed consent form must include “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.”

9.3 Additional Elements of Informed Consent

Six additional elements of informed consent may apply to certain research activities. Current federal regulations can be found at 45 CFR 46.116(b) (1-6). When appropriate, one or more of the following elements of information shall also be provided to each subject:

Risks Involving Pregnancy

For research studies intending to enroll females of child bearing potential, the consent form must include “a statement that the particular treatment or procedure may involve risks to the subject or embryo or fetus if the subject is or may become pregnant, which are currently unforeseeable.” This also includes a statement regarding risk associated with impregnation by a male who is receiving study medication that might be transmissible to a female (whether she is or isn’t a participant in the study).

Termination of Participation by Investigator

The informed consent must include “anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.” This element would be required for the following foreseeable situations: failure to follow the investigator’s instructions, if a disease gets worse, or if the sponsor or FDA closes the study, or simply “at any time for any reason” that is both ethical and just.

Additional or Incurred Costs

The informed consent must include “any additional costs to the subject that may result from participation in the research.” This information would be included if there were additional costs incurred by the subject by participating in the study.

Subject's Withdrawal from Research

The consent form must include the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. This element would be required if the PI determined there is the potential for subjects to voluntarily withdraw from the study.

Consequences and Circumstances of Withdrawal

When appropriate, the Informed Consent form should state the consequences (e.g., medical/health) of a subject's decision to withdraw from the research. If applicable, the Informed Consent form should also state any anticipated circumstances (e.g., adverse reactions, non-adherence to protocol instructions) under which the subject's participation may be terminated by the investigator or sponsor without regard to the subject's wishes.

Disclosure of New Findings

The Informed Consent form must include “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.”

New Information and Continued Participation

In medical, dental, psychological research, etc., the federal regulations require the inclusion of a separate statement indicating that if new information, such as changes in the potential risk/benefit ratio, or new alternatives to participation develop during the course of the study that may affect a subject's willingness to continue participating, the subject will be informed promptly and may then decide whether to continue participating in the ongoing study. The IRB will advise the PI whether or not subjects should be asked to sign a revised Informed Consent form.

Number of Subjects:

The informed consent should include the approximate number of subjects involved in the study. This additional element is required for all UNTHSC research projects.

Other Additional Elements to be Considered

Cash or Cash Equivalent

Cash payments (if any) should be described in dollar amounts. Subjects should also be told how much of the payment they will receive if they do not complete the research. In compliance with the stated position of the Food and Drug Administration (FDA), UNTHSC encourages the adoption of a pro-rated payment system whenever possible. The nature, amount and method of payment or other remuneration must not constitute undue inducement to participate (e.g., the payment alone should not serve as sufficient inducement for the subject to volunteer). Reimbursement may be provided for costs of participation (parking fees, travel, lost time from work, baby-sitters, etc.). Therefore, partial participation in a research activity would obligate partial payment.

Academic Credit

If payment will be in the form of academic credit that will be awarded for research participation, the amount and type of credit should be clearly stated as well as any required conditions for credit.

Product Development

Investigators are required to inform subjects in the Informed Consent form if any human materials (tumor tissue, bone marrow, blood, etc.) may be used to establish a commercially useful product (e.g., a cell line). Subjects should also be informed that they may not benefit from the development of the product.

Sponsor or Funding Agency Identification

When appropriate, subjects should be told who is funding the research (e.g. drug company, device manufacturer, Contract Research Organization (CRO)).

9.4 Who May Conduct the Informed Consent Process

The federal regulations 45 CFR 46.116 state: “No investigator may involve a human being in research covered by this policy unless the investigator has obtained legally effective informed consent of the subject or the subject’s legally authorized representative. An investigator shall seek such consent only under the circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.” Further, a basic element that is to be included in a consent document is “an explanation of whom to contact for answers to pertinent questions about the research...”

Therefore, the following is the UNTHSC policy on who can conduct the informed consent process for human research studies:

- Individuals who are knowledgeable about the protocol must obtain consent from subjects for participation in a study. Specifically, they must be able to describe the purpose, procedures, benefits, risks, and alternatives to participation in the study. They must be able to answer subjects' questions about the protocol;
- Essentially, anyone who is consenting subjects is classified, for the purposes of the protocol, as "key personnel";
- Sometimes more than one person on the research staff participates in the consent process. For example, nurse coordinators may describe the study procedures and a physician investigator may discuss specific issues related to the medical interventions and potential alternative treatments;
- All individuals who participate in the informed consent process must first successfully complete the required educational training on the protection of human research subjects (see Section 8.2 for more detail).
- The PI must inform the IRB about those individuals who will obtain consent from subjects, and attest that they meet the above criteria. The individuals must be listed in the protocol and/or IRB application, or should be added to key personnel using the Application for Change in Key Personnel form (see Appendix C)
- The PI is ultimately responsible for ensuring that ethically and legally valid consent is obtained from all research subjects;
- The investigator or other key personnel actually obtaining the informed consent must sign the study consent document(s) on the signature line labeled "Investigator's Signature / Person Obtaining Informed Consent" at the time consent is obtained;
- For consent that is obtained when an oral translator is used to assist subjects in understanding the research study, a witness signature is required. Additionally, the IRB may require a signature from a witness or advocate assuming a greater role (e.g., witness the entire consent process, serve as a child advocate, etc.);

9.5 Legally Authorized Representative

For studies involving cognitively-impaired adults, consent guidelines and the use of legally authorized representatives are governed by other principles and procedures. For more information, refer to the "Cognitively-Impaired Persons" section in Chapter 12. If studies relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and

conditions of research subject's, consent must be sought from the surrogate decision makers based on state and federal laws.

Adequate provisions should be made for soliciting the independent, non-coerced assent from children or cognitively-impaired persons who are capable of a knowledgeable agreement. If the person from whom assent is sought refuses to participate, the person should not be enrolled, even if the parent or authorized representative gives permission. (The IRB may make an exception to this guideline in studies of children with life-threatening illnesses who are eligible for research treatment protocols.) Alternatively, if the person from whom assent is sought agrees to participate, the person may not be enrolled if the parent or authorized representative does not give permission. In rare circumstances, depending on the nature of the study and the age and circumstances of the minor, the IRB may waive the requirement for parental or authorized representative's permission.

9.6 Documentation of Informed Consent

The purpose of an Informed Consent document (form) is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the written Informed Consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the executed Informed Consent form must be given to the subject. Unless the investigator has requested a waiver of documentation of consent, the subject's signature on an Informed Consent form is required prior to beginning any study procedures. The witnesses' signature (where applicable) attests that the subject voluntarily signed the Informed Consent form and validates the subject's identity. It is recommended that the witness be an unbiased third party.

No investigator may involve a human being as a subject unless the researcher has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject (or representative) sufficient time to consider whether or not to participate and under circumstances that minimize the possibility of any coercion. Information given to the subject or the representative shall be in a language understandable to the subject or representative.

No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or to appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

When deception is used as a technique in research, there should be a prompt and complete debriefing of the subjects. Debriefing may include explaining the research, and if possible, providing the opportunity for withdrawal of personal responses or withdrawal from

participation in the study. A debriefing statement for IRB review should be submitted along with the Informed Consent form.

The Informed Consent form signed by a study subject or the subject's legally authorized representative must be an exact copy of the form that is approved by the IRB and bear the appropriate date stamp of the IRB. The Principal Investigator or research staff must not write or attach additional information to the consent form, unless specified in approved protocol or approved by IRB. One copy must be given to the research subject and the original consent with the original signature must be maintained by the investigator. Another copy of the Informed Consent form must be maintained in the subject's research chart, medical record (unless otherwise restricted), or equivalent file in all relevant research studies. Sample Informed Consent templates are available on the appropriate OPHS/IRB website at: <http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Forms>

By following the sample template language, the investigator ensures that the basic and additional elements of consent as required by the federal regulations are included.

9.7 Waivers for Informed Consent

Waiver of Documentation of Consent

In some situations, the IRB may waive the requirement for obtaining a signed Informed Consent form 45 CFR 46.117(c). Investigators may request that the IRB waive the requirement for a signed, written, Informed Consent form. The IRB may waive the requirement for a signed consent if it finds:

1. The only record linking the subject and the research would be the Informed Consent form and the principal risk would be potential harm resulting from a breach of confidentiality (e.g. the subjects would be placed at risk by documents linking them with an illegal or stigmatizing characteristic or behavior), and the research is not subject to FDA regulations. Each subject will be asked whether they want documentation linking them with the research, and the subject's wishes will govern; **or**
2. The research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research (the documentation may also be referred to as an "information sheet"). Examples of types of studies that fall into the first category are survey or interview studies that contain highly sensitive (e.g., criminal behavior, sexual behavior) questions. Examples of studies that fall into the second category are mailed surveys about topics that could not reasonably damage a subject's reputation, employability or be otherwise stigmatizing.

Waiver of documentation of consent can mean no written document is provided to the subject. For example, with a random-dial telephone survey study, the telephone interview would begin with a script that includes all of the required elements of consent, but the study subjects would receive no written information about the study either before or after the interview. The telephone script containing the elements of consent must be included in the research application and reviewed and approved by the IRB. Or, the waiver of documentation of consent can mean the subject's signature does not have to be obtained. IRB regulations stipulate that the IRB Chair may still require that the investigator provide the subject with a written statement about the research when granting a waiver of documentation. For example, in a mailed-out survey study or in an Internet-based survey, the Chair may determine that it is reasonable for the investigator to provide the subjects with an information sheet containing all of the basic elements of consent. The information sheet would state that returning the survey or questionnaire via mail or the Internet, or responding to the interview questions, constitutes the subject's consent/agreement to participate in the research study.

OHRP Human Subject Regulations Decision Chart 10 provides more information.

Waiver of Elements of Consent or Consent Itself

Some research projects would not be possible if informed consent from subjects were required. The IRB may approve a consent procedure that does not include, or which alters, some or all of the elements of informed consent, or may waive the requirements to obtain informed consent. The IRB may consider waiving the requirement for some or all of the elements of informed consent 45 CFR 46.116(d). The regulations state that informed consent may be waived in full or in part if the IRB determines that:

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

Examples of types of studies in which all of the elements of consent have been waived include retrospective chart reviews, or studies of existing pathology specimens (all specimens to be studied have already been collected and are "on the shelf" at the time of the IRB application). Presuming that the study can be classified as minimal risk and that adequate provisions for protecting the confidentiality of the data are in place, the IRB Chair generally finds that obtaining consent is not possible.

Examples of types of studies in which some of the elements of consent have been waived include certain types of ethnographic research, and studies utilizing deception. For example, in a minimal risk study involving playing a computer game to test subjects' responses to differential payoffs or reinforcements, the investigator might indicate in the Informed Consent form that the purpose of the study is to test reaction time. This deception may be necessary because the study would be compromised if subjects were told the true purpose. In this scenario, one of the basic elements of consent – the purpose of the study – could be waived by the IRB Chair, and not included in the Informed Consent form. It should be noted that studies involving deception require a debriefing statement that would be provided to the subjects (written and oral) at the conclusion of the study procedures. OHRP Human Subject Regulations Decision Chart 11 (see Appendix E) provides more information.

Investigators requesting a Waiver of Informed Consent or a Waiver of Documentation of Informed Consent should complete the appropriate OPHS/IRB Forms and submit them with the IRB application. The forms are available on the OPHS website at:

<http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Forms>

9.8 HIPAA Authorization Addendum

For those projects involving protected health information (PHI), an updated Health Insurance Portability and Accountability Act (HIPAA)-compliant authorization addendum must be attached to the informed consent. The subject must sign and date both the authorization and the Informed Consent form. A HIPAA template addendum can be downloaded from the OPHS website at: <http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=IRB%20Forms>

The HIPAA Authorization can be a separate document from the Informed Consent Form or can be incorporated into the body of the consent form. OPHS recommends that it be a separate document as presented in the HIPAA Authorization Template.

For more information on HIPAA Authorization and compliance with such rules and regulations, see Chapter 16 “Health Insurance Portability and Accountability Act (HIPAA).”

9.9 Obtaining Consent from Non-English Speaking Subjects

Section updated on 7/19/11 to modify the procedures for Spanish translation verification by OPHS.

If a study includes non-English-speaking subjects, the protocol must reflect the methods for assuring full understanding, possibly with the assistance of an interpreter and by using the short form consent described below. However, when the investigator anticipates enrolling non-English speaking subjects, a translated version of the IRB-approved Informed Consent form must also be submitted to the IRB for review. In addition, it is important for someone on the research team to be fluent in the subject's language to answer questions and address concerns.

Policy for Translation of Consent Forms into Languages Other than English

When the study subject population includes people who do not understand English, and the investigator or the IRB anticipates that consent interviews are likely to be conducted in a language other than English, the IRB will require translation of the consent documents that accurately convey the information as approved by the IRB.

The use of translated consent forms in a research project implies that a potential subject will not speak or read English well enough to comprehend the nature or specifics of the research study. For example, a person who speaks “Spanish only” would be such a subject needing translation services. The translation of a consent form is not enough in this situation; someone on the research team should be able to effectively communicate the various aspects of the project to that subject. This is especially critical if the subject has questions or wants to communicate a “real time” concern during study procedures. Thus, someone on or affiliated with the research team needs to be fluent in that language. Translating documents is a good starting point, however, recall that consent is an ongoing process, and not simply a signed document.

Translation Services

At UNTHSC, OPHS does not offer translator services to investigators. Investigators (or sponsors) are responsible for having their own documents translated into the appropriate language. Once an investigator has a translated document (and related subject interactive process) in place, OPHS is available to assist with verifying the accuracy of the translation (currently for Spanish documents) or the investigator can arrange for their own translation validation by having the translator sign a translation affidavit on the “Consent Document Translation Affirmation Form” (see Appendix C) to that effect. The statement should be notarized.*

If an investigator requests a Spanish language document be reviewed and verified by OPHS, and such request is granted, no notarized affidavit from the translator needs to accompany the IRB submission of the Spanish-translated document. Instead, the Spanish document can be submitted with only a signed memo or “Consent Document Translation Affirmation Form” by the translator. OPHS will review the document for accuracy and, if no changes or clarifications are warranted, OPHS will sign a “Translation Verification Letter”, which will be incorporated into the final IRB packet for review and approval. This letter will serve as proof of an appropriate second-party review for translation accuracy.

Note that this OPHS-provided Spanish-translation verification service is available only if resources and staff time permit and only for UNTHSC employees conducting the original translation. All outsourced translations require a notarized statement upon submission (see * below).

It is important for investigators to obtain UNTHSC IRB approval of the English versions of the forms requiring translation prior to sending the documents to be translated.

If the study sponsor will provide the translation services, the investigator should obtain IRB approval of the English version of the forms before sending them to the sponsor/sponsor's translating service to be translated.

Once translated, the forms should be re-submitted to OPHS for review and approval with a completed and signed "Consent Document Translation Affirmation Form." All translated forms should be accompanied with an IRB approved English version to assist with OPHS review. Investigators are responsible for obtaining their own translation services. Please contact OPHS staff for guidance in this area.

*Notarization is required to verify the identity of the translator. However, if the translation is done by a UNTHSC employee, notarization is not required. However, a signed translation affidavit on the "Consent Document Translation Affirmation Form" or a signed memo from the UNTHSC employee conducting the translation is still required as documentation of translation competence and performance.

Guidelines for the Use of the Short Form

If there is occasional need for other languages (i.e. languages other than English), the *short form* consent will be used in addition to the IRB-approved English version of the (longer) Informed Consent Form, which will be orally translated into the target language by a translator. Although the *short form* is characterized to be a more "condensed" version of the full (longer) written informed consent version, the *short form* must contain the same core/basic elements and possibly additional elements found in the IRB-approved English version (e.g. purpose of research, research procedures, potential risk/benefit ratio, contact information, etc.).

When to use a Short Form:

OPHS-IRB recommends that studies involving a study population or location in which subjects are non-English speaking or where the study design for subject enrollment provides sufficient time to translate the informed consent and receive IRB approval for it, a *short form* should NOT be used. In these cases, use a properly translated regular long (complete) IRB-approved consent document.

However, the following are circumstances in which a Short Form *can* be used:

- The subject or subject's representative does not understand or speak English.
- The subject or subject's representative speaks a language not originally anticipated in the study protocol.
- A translated consent form (i.e. in language understandable to subject) has not been approved by the IRB. Note that the short form has to be reviewed and approved by the IRB before implementation; therefore,

non-English speaking subjects cannot be consented prior to IRB review and approval.

- There is not sufficient time for the preparation of a properly translated written informed consent and IRB review of such document.

Process for Consenting Subjects with a Short Form:

- A translator must orally translate the IRB-approved English version of the Informed Consent into language understandable to the subject.
- A copy of the short form must be given to the subject to read after the oral explanation/translation of the study is given. Thus, subjects can verify that all points outlined in the short form were covered by the person obtaining consent. Note that the short form must be in language understandable to the subject (i.e. in the target language).
- Only the short form is to be signed and dated by the subject or the subject's representative.
- A witness who is both fluent in English and the target language is required to sign the short form and the English version of the Informed Consent Form; thereby, attesting to the validity of the translation. A witness can also act as the translator.
- The IRB-approved English version of the Informed Consent must be signed by the person authorized by the IRB to obtain subject consent. Note that the person obtaining consent can also act as the translator. A separate person acting as a witness still needs to be present to verify the interpretation (oral translation) of the consent process. Basically, besides the subject, at least two different people need to be involved in the process of consenting: one the consenter, and another as a witness.
- Finally, a copy of the signed short form and IRB approved Informed Consent (English version) must be given to the subject or the subject's representative.

OHRP and FDA Guidelines:

For OHRP and FDA guidelines for translation of consent forms, please refer to:

<http://www.hhs.gov/ohrp/humansubjects/guidance/ic-non-e.htm>

<http://www.fda.gov/oc/ohrt/irbs/informedconsent.html#nonenglish>

<http://www.fda.gov/oc/ohrt/irbs/informedconsent.html#documentation>

9.10 Child Assent Special Requirements

Section 9.10 was modified on 2/1/10 to include additional information about re-consenting minors who become adults during a research study.

Capability of Assenting

The IRB shall determine that adequate provisions are made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent. “If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or that the intervention or procedures involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children, and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.”

Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances, in which consent may be waived in accord with §46.116 of Subpart A. The assent form is used when the investigator recruits subjects who, by age or circumstance, are not able to give legally effective informed consent. Minors/children by definition cannot give legal consent. When legally effective informed consent cannot be obtained, the investigator should, when appropriate, obtain the "assent" of the minor/child subject. The assent form documents the minor subject's knowledgeable agreement, or assent, to participate in a research project. The investigator should respect the decision of a minor/child subject not to participate, even when the parent or legally authorized representative gives permission, unless permission to include the minor/child subject without assent is specifically requested from the IRB. For studies involving minors/children, OPHS recommends that the assent form be used with the 7-12 age range, but it may also be used with teenagers to enhance their comprehension if the study involves complicated procedures. An assent template is available on the OPHS/IRB web site.

Assent Form Requirements for Permission by Parents 45 CFR 46 Subpart D (Research with Minors)

Subpart D of the federal regulations, concerning research with children/minors, is very explicit about consent requirements. Some situations require permission from at least one parent, while other situations require permission from both parents. In other cases, waiving the requirement to obtain consent may be necessary. IRBs need to carefully review proposals involving children to ensure adequate protections have been put in place. The IRB Checklist for research involving minors/children serves as a guide during the IRB review process.

The Four D Subparts

§46.404 Research Not Involving Greater than Minimal Risk

“Health and Human Services (HHS) will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate

provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.”

§46.405 Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subjects

“HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

- a) The risk is justified by the anticipated benefit to the subjects;
- b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.”

§46.406 Research Involving Greater than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition

“HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- a) The risk represents a minor increase over minimal risk;
- b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.”

§46.407 Research Not Otherwise Approvable Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Children

“HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

- a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

- b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
1. That the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:
 - (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - (ii) the research will be conducted in accordance with sound ethical principles;
 - (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.”

Requirements for Parental Signature and Waiving Consent: Permission of One Parent

The IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 (research not involving greater than minimal risk) or §46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects).

Permission of Both Parents

Where research is covered by §46.406 and §46.407, permission is to be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Waiver of Consent Requirements

If the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in 45CFR46 Subpart A and 45CFR46.408 paragraph (b), provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law.

When Minors become Adults (during a research study)

Participants who are enrolled in a study as a minor (Texas state law considers a “minor” to be an individual under the age of 18) should be re-consented as adults when they turn 18 years old if they are still participating actively (receiving intervention, test article, surveys) in a

study. Therefore, investigators conducting research with children, particularly adolescents, should come up with an appropriate plan for re-consenting children who become adults while participating. The plan for re-consenting minors should be described in the protocol synopsis (see OPHS-IRB and below website for guidance and recommended language). Additionally, it should be mentioned that minor participants will be re-consented as adults when they turn 18 years of age in the parental permission form and the child/adolescent assent form.

http://www.hsc.unt.edu/sites/OPHS-IRB/index.cfm?pageName=Instructional%20Guidelines#consenting_HRS

9.11 Consenting Subjects Who Are Unable to Read or Speak

Section 9.11 was modified to the OPHS-IRB Manual on 2/15/13

The purpose of this guidance is to explain how researchers should obtain and document informed consent for subjects who:

1. Understand English but cannot read due to blindness or illiteracy, or
2. Understand English but cannot talk or write due to incapacitation.

The governing principles of human subject research: **respect for persons, beneficence, and justice**, require that researchers not exclude subjects based solely on their inability to read or speak. Investigators need either to communicate directly with subjects, or to provide a reliable alternative to ensure that:

1. Study participation is **voluntary**, as indicated by free and truly informed consent (respect for persons); and
2. Study **schedules, procedures, and risks are accurately communicated**, and subjects have ongoing opportunities to express concerns and ask questions, in order to minimize risks to subjects (beneficence); and
3. There are fair **procedures and outcomes in the selection of research subjects** so that risks and benefits of research are shared in society (*justice*).

The medical and technical information discussed during the initial consent discussion, as well as ongoing, study-related information, can be very complex and should be communicated to subjects through a staff member with training and understanding in medical terminology. In addition, an individual with a professional commitment to maintain strict confidentiality should handle the private medical issues discussed with subjects.

The Informed Consent Discussion with Legally Blind Subjects

If you are enrolling subjects who cannot read the consent materials due to blindness, or the subject's legally authorized representative is legally blind:

- It is recommended that an impartial witness observe the consent process.
- The IRB-approved consent form should be presented orally.
- Sufficient time should be allowed for questions to be asked and answered, both by the subject, and by the person obtaining consent to ensure the subject comprehends the consent information.

If the subject (or subject's legally authorized representative) verbally agrees to participate in the study:

- If capable of doing so, the subject signs and personally dates the consent form. This signature can be in any symbolic mark or form the subject chooses.
- The witness (or representative of the subject) signs and personally dates the consent form. By doing so the witness attests that the consent information was accurately explained and that the subject appears to understand the information, and that informed consent was given freely.
- The person obtaining consent signs and dates the consent form.
- A copy of the consent document is given to the subject.

The Informed Consent Discussion with Illiterate Subjects

If you are enrolling subjects who cannot read the consent materials due to illiteracy:

1. It is recommended that an impartial witness observe the consent process.
2. Consent materials should be presented orally.
3. Sufficient time should be allowed for questions to be asked and answered, both by the subject, and by the person obtaining consent to ensure the subject comprehends the consent information.
4. If capable of doing so, the subject signs, or places their chosen symbolic mark to signify consent.
5. The witness signs and personally dates the consent form. By doing so the witness attests that the consent information was accurately explained and that the subject appeared to understand the information, and that informed consent was given freely.
6. The person obtaining consent signs and dates the consent form.
7. A copy of the consent document is given to the subject.

The Informed Consent Discussion with English-Speaking Subjects Who Cannot Talk or Write

To enroll subjects who understand English but who are unable to talk or write due to physical limitations, investigators must assess the subject's ability to understand the consent materials and to indicate their wish to participate or not. The subject may be entered into the study if the person:

1. retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent), and
2. is able to indicate approval or disapproval to study entry

Informed consent should be obtained and documented as follows:

1. An impartial witness should be present during the entire consent discussion.
2. The IRB-approved consent form should be presented orally and clearly explained by the person obtaining consent.
3. Sufficient time should be allowed for questions to be asked if the subject is capable of doing so. The person obtaining consent should ask questions to ensure the subject comprehends the consent information.
4. If the subject indicates agreement to participate in the study, informed consent should be documented as follows:
 - The consent form should be annotated by hand to describe the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.
 - Consider using a video tape recording to further document the consent discussion.
 - The witness signs and personally dates the consent form. By doing so the witness attests that the consent information was accurately explained and that the subject apparently understood and informed consent was given freely.
 - The person obtaining consent signs and dates the consent form.

9.12 Re-Consenting Subjects

Section 9.12 was added to the OPHS-IRB Manual on 2/1/10

Federal regulations do not require re-consenting of subjects who have *completed* their active participation in the study, or of subjects who are still actively participating, *when the proposed change will not affect their participation*. However, when changes do occur in the conditions or the procedures of a study that would affect an individual subject, the investigator should once again seek informed consent from the subjects. Those subjects who are presently enrolled and actively participating in the study should be informed of the change and re-consented if it might relate to the subjects' willingness to continue their participation in the study. Adverse events may occur during a research activity that would directly affect whether prospective or enrolled subjects would wish to continue in a particular research activity. The IRB does not require a subject re-consent at the time of the protocol continuation approval, *unless there have been modifications to the consent form that would affect an individual subject*. Study participants who are minors and actively participating in a study should be re-consented as adults when they turn 18 (see Section 9.10 for detailed information).

Chapter 10: Privacy and Confidentiality

CHAPTER CONTENTS

- Privacy
- Confidentiality

Overview

This chapter pertains to the importance of privacy and confidentiality protections as required under the Common Rule 45 CFR 46.111, Food and Drug Administration (FDA) regulations 21 CFR 56.111, and state and local laws. The IRB ensures the privacy of subjects and the confidentiality of data by reviewing each study carefully to assure adequate consideration is given to these issues. This chapter also contains information on Certificates of Confidentiality issued by the National Institutes of Health (NIH).

Definitions

- Privacy: Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.
- Confidentiality: Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.

Privacy and confidentiality are supported by two of the three principles of research ethics identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in The Belmont Report: (a) respect for persons and (b) beneficence. Respect for persons requires that subjects be allowed to exercise their autonomy to the fullest extent possible, including the autonomy to maintain their privacy and to have private information identifying them kept confidential. Beneficence requires that risks to subjects are minimized, benefits are maximized, and risks to subjects do not outweigh the benefits to

subjects and others. The maintenance of privacy and confidentiality helps to protect subjects from a variety of potential harms, including psychological distress, loss of insurance, loss of employment, or damage to social standing that could occur as the result of invasion of privacy or a breach of confidentiality (Amdur & Bankert, 2006).

IRBs must consider the protection of privacy and confidentiality as part of their ethical and regulatory duty to protect the rights and welfare of human subjects.

Although privacy and confidentiality are difficult to define in practical terms, and are viewed differently by different individuals, IRBs can successfully apply them to research on a case-by-case basis. The IRB must consider both privacy and confidentiality for each segment of the research, from subject recruitment through follow-up and maintenance of the research records after the study has been finished.

Often, particularly in behavioral research, the main risk to subjects is the possibility of invasion of privacy or a breach of confidentiality. In the consent process, subjects must be informed of the precautions that will be taken to protect the confidentiality of the subjects' information and also informed of the parties who will or may have access to the information. This will allow subjects to decide whether they agree with the IRB's assessment that the human subject protections are adequate (Amdur & Bankert, 2006).

IRB review of privacy and confidentiality protections is required under the Common Rule and the FDA regulations, as well as state and local statutes. Protections reviewed by the IRB include:

- Adequacy of promises to subjects on Informed Consent Forms;
- Privacy/data protections during recruitment and follow-up;
- Evaluations of methods to be employed to protect data and samples during storage and use;
- Eventual data destruction (if promised);
- Divulge sponsor/legally authorized access to subject information

The IRB must decide on a study-by-study basis whether there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. The IRB must take into account the degree of sensitivity of the information that may be obtained in the research, and the protections offered to the study population. As with other aspects of IRB review, these determinations will be dependent on the circumstances of the study and subjects. Coded information, de-identified information and cultural differences in value systems must be understood by the IRB for study approval.

State Laws Addressing Privacy and Confidentiality

IRBs must consider state laws concerning privacy and confidentiality when reviewing research. These may take the form of either statute or case law. The Common Rule and FDA regulations require the IRB to be able to ascertain the acceptability of proposed research in terms of “applicable law”, which includes state law. The Common Rule and FDA regulations also clearly state that other laws are not preempted by the federal regulations and continue to apply. Therefore, any state laws that require greater protections for subjects than the Common Rule and FDA regulations continue to apply.

10.1 Privacy

The IRB requires investigators, or other relevant parties, to explain how privacy and confidentiality of the information obtained in the course of the study will be maintained. Investigators are required to provide this information in the IRB application and in the protocol. The application must contain plans for maintaining privacy and confidentiality, which can include storing records in locked file cabinets, in locked offices, on computers protected by a password, or on computers that are not linked to a network.

The IRB must consider the protection of privacy and confidentiality during the subject recruitment process. The manner in which subjects are identified and approached for participation in research may constitute an invasion of privacy or confidentiality. Another potential breach of privacy is the collection of sensitive information during the screening period and subsequent retention of the information without consent from the subject.

For research involving particularly sensitive information, such as drug abuse, the IRB may also require that the investigator obtain a federal Certificate of Confidentiality to protect the research records from release in any federal, state, local civil, criminal, administrative, legislative, or other proceeding. The Informed Consent Form must accurately provide the subject with information concerning the confidentiality of research records.

10.2 Confidentiality

Issues of confidentiality should be particularly scrutinized in research conducted over an extended period of time. Some longitudinal studies extend for periods of 10 or more years. Likewise, many oncology studies can include subject follow-up until death. During the course of such a study, the subject’s values and circumstances can change greatly, causing changes in the importance of privacy and the confidentiality of records. The investigator must describe sound plans to protect the subject's identity as well as the confidentiality of the research records. Care should be taken to explain the confidentiality mechanisms that have been devised. For example, the use of numbering or code systems or safely locked files in private offices would suffice for such an explanation. Furthermore, the investigator should describe who has access to the data and under what circumstances a code system may be broken.

Without appropriate safeguards, problems may arise from long-term retention of records. In special circumstances requiring additional safeguards to prevent potential criminal prosecution

of the participating human subject, the IRB may require the destruction of all data that can identify the subjects.

Subjects should be informed whether the data collected will be retained, and, if so, for what purpose, what period of time, or whether and when data will be de-identified and destroyed.

A special situation arises for video or taped data and photographs (when not used for transcription purposes) since these media provide additional potential means for subject identification. Investigators must secure subject consent explicitly mentioning these practices. They should also explain plans for final disposition or destruction of such records.

The following UNTHSC recommended language should be incorporated into the protocol synopsis, and can be modified as appropriate for each IRB submission.

“Research data, in hard copy or electronic form (CDs, DVDs, digital or magnetic tape, hard-drives, flash-memory drives, etc.) will be stored and managed in a secure manner following NIH guidelines and according to state and institutional policies and practices. Further, hard copy documents containing subject data, identifiers and linked data will be stored in secure document containers (file cabinets, lockers, drawers, etc.) in accordance with standard document management practices. At all times, only listed key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct.”

NIH Certificate of Confidentiality (From NIH Office of Extramural Research website)

A Certificate of Confidentiality is a document issued by the NIH to protect the privacy of research subjects enrolled in “sensitive” research by protecting investigators and institutions from being compelled to release information that could be used to identify subjects in a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

Certificates can be used for biomedical, behavioral, clinical or other types of “sensitive research.” Sensitive means that disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. Examples of sensitive research activities include but are not limited to the following:

- Collecting genetic information;
- Collecting information on the psychological well-being of subjects;
- Collecting information on subjects' sexual attitudes, preferences or practices;

- Collecting data on substance abuse or other illegal risk behaviors;
- Studies where subjects may be involved in litigation related to exposures under study (e.g., breast implants, environmental or occupational exposures).

By protecting investigators and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help the investigator achieve the research objectives and promote participation in studies by assuring privacy to subjects.

A Certificate of Confidentiality <http://grants1.nih.gov/grants/policy/coc/index.htm> protects personally identifiable information about subjects in the research project while the certificate is in effect. Generally, certificates are effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The expiration date should correspond to the completion of the study. The certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the certificate is in effect. An extension of coverage must be requested if the research extends beyond the expiration date of the original certificate. However, the protection afforded by the certificate is permanent. All personally identifiable information maintained about subjects in the project while the certificate is in effect is protected in perpetuity.

While certificates protect against involuntary disclosure, investigators should note that research subjects might voluntarily disclose their research data or information. Subjects may disclose information to physicians or other third parties. They may also authorize in writing the investigator to release the information to insurers, employers, or other third parties. In such cases, researchers may not use the certificate to refuse disclosure. Moreover, researchers are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases http://grants1.nih.gov/grants/policy/coc/cd_policy.htm or subject's threatened violence to self or others. However, if the investigator intends to make any voluntary disclosures, the Informed Consent Form must specify such disclosure. In the Informed Consent Form, investigators should tell research subjects that a certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above.

The investigator may choose to apply for a Certificate of Confidentiality on their own or the IRB may require that an investigator obtain a certificate prior to conducting the research. Investigators who intend to apply for a Certificate of Confidentiality should contact the OPHS regarding procedural steps for IRB approval and communicating with the NIH. Complete information is available on the NIH Office of Extramural Research website.

For purposes of this policy, the Director, OPHS is the designated UNTHSC organizational official authorized to sign requests to NIH for a Certificate of Confidentiality involving UNTHSC personnel and projects.

Confidentiality in the Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed Informed Consent Form for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the Informed Consent Form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Confidentiality in the Waiver of Consent

In some instances, under certain circumstances, federal regulations permit the IRB to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided that the IRB finds and documents that:

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

It is important to note that numbers 1-4 must all apply and must be cited as justification of waiver of informed consent. For example, under item 4 (above), there may be new information as a result of a survey or focus group that would be relevant to all subjects.

An investigator who qualifies for an alteration of federal required elements of consent must still disclose to subject pertinent study information. This consent can be in form of a recruitment/cover letter, which includes a brief study explanation and procedures. The letter should also include a brief statement about:

1. Risks associated with the study

2. Option to withdraw
3. Voluntary participation
4. Confidentiality, and
5. Appropriate contact information (principal investigator and IRB Chairman)

If a research study qualifies for a waiver informed consent, the UNTHSC-IRB requires an investigator to have an oral or written script containing core information about the research study.

Confidentiality Requirements for IRB members, Consultants, Advisors, Observers

IRB Reviewers, Consultants, Advisors, *ex officio* personnel, and other with appropriate and authorized access to protocol documents must also maintain a high degree of confidentiality. Such persons are required to sign and honor a Confidentiality Agreement. And, as with investigators conducting research involving human subjects, IRB Reviewers, Consultants, Advisors, *ex officio* personnel, and other with appropriate and authorized access to protocol documents must behave with due diligence and respect for privacy and confidentiality. See Section 4.10 for specifics on these requirements.

Chapter 11: Subject Compensation and Recruitment Issues

CHAPTER CONTENTS

- **Compensation**
- **Recruitment**
- **Payment Agreements for Industry Sponsored Studies**
- **Payments for Referrals (Finder's Fess) Are Not Permitted**
- **Payments to Accelerate Recruitment Are Not Permitted**

Overview

Subject compensation and recruitment issues are significant concerns of the IRB. Compensation must not be excessive or coercive. Advertisements must reflect the true nature of the research and not mislead potential participants. This chapter explores these issues and discusses criteria for advertisements and payment agreements with Industry sponsored studies.

11.1 Compensation

Compensation for participation in research remains a contentious issue with no official guidelines. Some believe all research should be truly voluntary and without financial remuneration. Others hold that participating in research requires time and effort, which can be rewarded financially as well as altruistically. Many papers have been written about subject compensation and guidelines have been suggested.

In general, payment for participation in research should not be offered as a means of coercive persuasion (or unduly influential). Rather, payment should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Accordingly, compensation may not be withheld contingent on the subject's completion of the study. In most cases involving continued participation, compensation should be given on a reasonable, prompt, and prorated basis to avoid possible coercion. The payment should be made

throughout the course of the study, contingent on the procedures in which the subject participates.

Compensation should be appropriate to the time and/or procedures involved.

Compensation can be provided in numerous ways, including cash, gift certificates, gift cards, parking reimbursements or public transportation passes, meal coupons, nominal gifts, or school supplies.

Excess compensation is especially problematic in greater than minimal risk studies, where compensation can be unjust by appealing to economically disadvantaged subjects.

The appropriate amount of payment for participating in research requires much consideration by the Principal Investigator (PI) as well as the IRB. The IRB allows the PI to provide subjects with a payment of a small proportion (usually not to exceed 40% of the total compensation) as an incentive for the completion of the study only when such incentive is itself not coercive.

11.2 Recruitment

Advertisements

Advertisements seeking human subjects are commonplace. Ads for research are found in newspapers, posters, public transportation, the internet, television, hospitals, and labs. They are heard on the radio and viewed on television. Nationally, new industries of patient recruitment firms and market research companies have created elaborate marketing packages. Recruitment materials coming from these packages – including brochures, flyers, advertisements, audio tapes, video tapes, and letters to potential subjects must not contain coercive language or incentives. The information provided in advertisements should accurately present the purpose of the research study and/or procedures. IRBs must review and approve all recruitment materials prior to use. To assure that recruiting methods and materials are not coercive, misleading or unduly influential, the IRB must review and approve all such materials being they can be implemented. The IRB must review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. In addition, the IRB must review all finalized audio/video advertisements for broadcast. The IRB may require changes to wording. Therefore, it is recommended that advertisement text be submitted for review well before the final taping occurs or the promotional/recruiting products are developed.

Federal regulations require that the IRB review and approve all recruitment materials for research subjects (e.g., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study) **prior** to implementation. Recruitment materials include, but are not necessarily limited to:

- Newspaper Ads, Posters, Flyers, Pamphlets

- Radio
- TV
- Internet Web Sites*
- Institutional e-mail and Publications
- Bulletin Boards
- Telephone Screening Scripts and/or Call Centers
- National Ad Campaigns
- Press Releases
- Organizational Listserv Mailings
- Physician to Patient Letters and Physician to Physician (Referral) Letters (e.g. mass mailings)
- Presentations to describe the project to Local Support Groups, Social Groups, Clinic Sites, Health Fairs, Grocery Stores, etc.

*Investigators may use the internet as a recruitment tool in several ways. However, online research advertisements containing more detail (including those posted on the UNTHSC intranet) will require prior IRB review and approval.

Online Listing of Clinical Trials (clinicaltrials.gov)

It is appropriate to add a study to a list of research studies (such as clinicaltrials.gov). In fact, investigators are encouraged and may be required by agencies and sponsors to list their clinical trials on such internet information sites. However, before any clinical trial initiated with UNTHSC as the sponsor can be listed on such sites, that protocol must have (a) prior UNTHSC IRB approval and (b) formal approval from the UNTHSC Office of Clinical Trials.

Recruitment materials should be submitted to the IRB for review along with the **initial** protocol submission.

For changes in recruiting materials, investigators should submit any new /additional recruitment materials or advertisements created after the initial approval of a study for IRB review and approval prior to their use. Revisions to IRB approved recruitment materials should be submitted for IRB review and approval prior to implementing the changes. Note that, in most cases, review of modified or additional recruiting materials can be conducted on an Expedited review basis, thus minimizing possible delays.

Federal regulations consider advertising for study subjects to be essentially the beginning of the informed consent process. Therefore, all advertisements (with the exception of those specifically approved for other health professionals or specialized audiences) *must be at an appropriate reading level, typically an 8th grade (US) level.*

Recruitment materials should include the following information:

- An honest and uncomplicated approach.
- The word “research” should be specified.
- The advertisement must indicate that the research study is being sponsored (or conducted at) the University of North Texas Health Science Center at Fort Worth.
- Statement of the condition under study and brief description of the purpose of the research.
- Brief summary of the eligibility criteria, including age range.
- A statement of the benefits.
- A statement of the approximate time commitment required.
- May include graphics or pictures appropriate to the purpose of the study.
- Contact person for further information, including telephone number (email address is also appropriate to include).
- When appropriate, the advertisement may state that subjects will be compensated or paid for participating (no dollar signs or specific dollar amounts). Recruitment materials that include dollar signs or specific dollar amounts may be considered on a case by case basis, and will require Full Board review. Investigators should consult with the IRB Chair to discuss this request prior to preparing the IRB submission

The following information should NOT be used in advertisements/recruiting materials:

- Specific dollar amounts or dollar signs (\$\$). Please Note: Investigators who wish to include specific dollar amounts in their recruitment materials should contact the IRB Chair to discuss their request. Review by the convened (Full Board) IRB will be required.
- Claims that a device or drug is safe and effective;

- The words “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational;
- Promises of “free medical treatment;”
- Compensation should not be excessive relative to the nature of the project.
- Statements or implications of certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
- Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device;
- Exculpatory language.
- Terms that may be offensive to the person reading the ad (i.e. “fat”, “old”, “naive”, etc.)

If your recruitment material is being submitted **after** IRB review of your initial protocol submission, you must attach a cover memo indicating how and where the ad will be used (e.g., run in local newspapers or magazines, a flyer posted in UNTHSC clinics, etc.). You should allow ample time for OPHS review and approval of your ad.

NOTE: Advertisements that will be published outside of UNTHSC (e.g., local newspaper, community newsletters, etc.) must also be reviewed and approved by UNTHSC Marketing. First, obtain IRB review and approval of the ad, then submit it to UNTHSC Marketing. If marketing makes any changes to the ad copy, re-submit the ad to the IRB for final review and approval before it “goes to press/radio, TV, etc.”

Advertising for subjects at UNTHSC by non-UNTHSC researchers

In some cases, research teams and investigators from other institutions (universities, hospitals, medical centers, etc.) may wish to advertise for or recruit subjects from the UNTHSC campus. Certainly, any research project involving human subjects that also involves UNTHSC faculty, staff or students as key personnel requires UNTHSC IRB review and approval. However, if there are NO key personnel from UNTHSC associated with the research project, recruiting ads do not need to be reviewed and approved by the UNTHSC IRB. However, such marketing and recruiting activities on-campus for non-UNTHSC projects may require approval from other units, such as Office of Research, Office of the President, various Department Heads and Deans, UNT Health, UNTHSC Marketing, etc. Non-UNTHSC researchers seeking to advertise and recruit at UNTHSC are encouraged to obtain appropriate permissions and approval from these other units before posting ads, flyers, handouts, etc. on campus.

11.3 Referral (Finder's) Fees for Recruitment of Research Subjects

Background

IRBs nationwide, as well as agencies, professional associations and organizations consider the use of special recruitment incentives in connection with clinical research, including finders' fees, referral fees, and recruitment bonuses to be unethical and representing a potential conflict of interest.

In general, such payments systems reward a member of the research team, or persons acting on behalf of the research team, in a manner not necessarily in the best interests of a subject or patient who may become a research subject. Such recruitment and enrollment incentive plans (whether they are money, gift or anything of monetary value above and beyond the actual cost of enrollment, conduct of research, and reporting on the results) constitute an unethical research practice. These incentive systems include, for example, finders' fees, referral fees, recruitment bonuses, an enrollment bonus for reaching an accrual goal, or similar types of payments.

Further, many commercial IRBs (including Western IRB, the largest commercial IRB in the country) do not allow physicians, study staff or subjects to offer or receive **referral fees** for research under their oversight. Their policy is in accordance with the American Medical Association Code of Medical Ethics (Policy # E-6.03) which states, "Offering or accepting payment for referring patients to research studies (finder's fees) is also unethical." Some states, including Texas, have laws that ban such practices for physicians, and by extension, persons acting on behalf of physicians.

In keeping with sound ethical practices, the IRB prohibits referral fees, finders' fees, recruitment bonuses and other special incentives, whether monetary or as gifts or goods and services, paid or given to persons conducting research involving human subjects, including but not limited to physicians, investigators, co-investigators, collaborators, coordinators, study staff, etc.

Note that it is acceptable for a research staff member to receive direct fair market value compensation for specific time and effort involvement engaged in the general recruitment process (i.e. hourly wage, percent effort, etc.); however, any *per capita* payment or fee for the recruitment of an individual subject is prohibited.

This policy does not prohibit payments, incentives or compensation made directly to a subject for his or her own participation and involvement as a research subject.

Enforcement

A violation of this policy will result in the specific protocol being suspended. Subsequent to this suspension, OPHS will initiate an investigation of all research protocols involving any member of the offending research team to determine how widespread this practice might be, and if any further suspensions might be justified.

Chapter 12

Chapter 12: Vulnerable Subject Populations

CHAPTER CONTENTS

- Children in Research (45 CFR 46, Subpart D and 21 CFR Parts 50 and 56)
- Pregnant Women, Human Fetuses and Neonates in Research (45 CFR 46, Subpart B)
- Prisoners in Research (45 CFR 46, Subpart C)
- Cognitively-Impaired Persons

Overview

This chapter explains the importance of including specific protections for children, pregnant women, fetuses, neonates, and prisoners as stated in the federal regulations. Federal regulations 45 CFR 46 Subparts B, C, and D are defined, describing the special precautions investigators must take when conducting their research:

B-Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research,

C-Additional Health and Human Services (HHS) Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects,

D-Additional HHS and FDA Protections for Children Involved as Subjects in Research.

IRBs and researchers must keep in mind that vulnerability extends beyond the regulatory definitions and vulnerability is an important factor in all IRB deliberations. Most individuals and classes of subjects may be vulnerable at some time during the study depending on the situation, condition, research, and the susceptibility to coercion. Investigators are also expected to take special precautions when including cognitively-impaired individuals in research.

12.1 Children in Research (45 CFR 46, Subpart D and 21 CFR Parts 50 and 56)

When children are involved in research, the regulations require the **assent** (knowledgeable agreement) of the child. When the IRB determines the children are capable of assenting, child assent must be obtained in addition to the **permission** of the parent(s) or guardian(s). The IRB determines whether all or some of the children are capable of assenting. Children should be asked whether or not they wish to participate in the research. The regulations do not specify a certain age at which assent must be sought, but, for most studies, the IRB suggests obtaining assent beginning at age 7. In certain studies, the IRB may determine assent from the child is unnecessary when the treatment for an illness or condition is only available in the context of the research. The approval of all research involving children must be documented according to 45 CFR 46 Subpart D and (when appropriate) 21 CFR Parts 50.

Helpful Definitions

Children: 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 state law considers any person under 18 years old to be a child.

Assent: A child's affirmative agreement to participate in research. Mere failure to object (absent affirmative agreement) should not be construed as assent.

Parent: A child's biological or adoptive parent.

Guardian: An individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

Permission: The agreement of parent(s) or guardian(s) to the participation of their child or ward in research.

Federal regulations permit IRBs to approve research projects involving children after determining which of the following categories applies, and only if the project satisfies all of the conditions in the applicable category:

45 CFR 46.404 and 21 CFR 50.51: No Greater Than Minimal Risk to Children Is Presented

The IRB finds that no greater than minimal risk to children is presented, and adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408/21 CFR 50.51.

The IRB determines whether both parents must give their permission unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child or whether the permission of one parent or guardian is sufficient.

The IRB generally finds that permission of one parent or guardian is sufficient.

45 CFR 46.405 and 21 CFR 50.52: Research Involving Greater Than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subjects

The IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

1. The risk is justified by the anticipated benefit to the subjects;
2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408/21 CFR 50.55.

The IRB determines whether both parents must give their permission unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child or whether the permission of one parent or guardian is sufficient.

The IRB generally finds that permission of one parent or guardian is sufficient.

45 CFR 46.406 and 21 CFR 50.3: Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge About the Subject's Disorder or Condition

The IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the subject's well-being, only if the IRB finds that:

1. The risk represents a minor increase over minimal risk;
2. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and

4. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408/21 CFR 50.55.
5. The IRB requires permission to be obtained from both parents/guardians, unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

45 CFR 46.407 and 21 CFR 50.54: Research Not Otherwise Approvable which Presents an Opportunity to Understand, Prevent, or Alleviate Serious Problems Affecting the Health or Welfare of Children

Research can be approved under this subpart when the IRB believes the research does not meet the requirements of 45 CFR 46.404, 45 CFR 46.405, 45 CFR 46.406 /21 CFR 50.51, 21 CFR 50.52, 21 CFR 50.53 and only if the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and the Secretary of HHS, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, has determined either:

1. The research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406/ 21 CFR 50.51, 21 CFR 50.52, 21 CFR 50.53 as applicable; or
2. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of any serious problems affecting the health or welfare of children;
3. The research will be conducted with sound ethical principles. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 45 CFR 46.408/21 CFR 50.55

The IRB requires permission to be obtained from both parents/guardians, unless one parent/guardian is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

How to Determine Whether an Individual is a Child when the Research is Conducted in Texas:

Texas law does not contain specific information about the participation of children in research studies. Therefore, it is recommended that investigators follow Texas healthcare law as described below.

Texas Definition of Children

In Texas, a person under the age of 18 years of age who has never been married, is not in the military, and has not been declared an adult by the court (i.e. had the disabilities of a minor removed) is considered a minor.

In Texas, no child under the age of 16 can become emancipated from their parents. Additionally, in Texas, no child under 18 can enter into a legal contract unless they are emancipated.

Emancipation through marriage or enlistment in the military usually requires parental permission in Texas.

Therefore, parental or guardian permission will be required for all non-emancipated minors who wish to participate in research in Texas.

Pregnant Children

Becoming pregnant and having a child does not automatically emancipate a minor in Texas. The minor will be responsible for the baby; however the parents will still be responsible for the minor. **Therefore, permission of the parent or guardian will be required for research that involves pregnant children under the age of 18 unless the minor meets one of the three criteria of emancipation mentioned above.**

According to Texas Law (Family Code Chapter 31), a child may go through a court procedure to request "Removal of Disabilities of a Minor." The minor may petition the court to have the disabilities removed for limited or general purposes:

1. A resident of the state of Texas;
2. 17 years or age, or at least 16 years of age and living separate and apart from the minor's parents, managing conservator, or guardian; and
3. Self-supporting and managing the minor's own financial affairs.

Research with Children who are Wards

According to federal regulations at 45 CFR 46.409 and 21 CFR 50.56, children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45.406 or 46.407 or 21 CFR 50.53 and 50.54 only if the research is related to their:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

Per federal regulations, the IRB will require the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as a guardian or in loco parentis (in the place of a parent). It is appropriate for the appointed person to serve as an advocate for more than one child.

As defined by federal regulations, the advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

12.2 Pregnant Women, Human Fetuses and Neonates in Research (45 CFR 46 Subpart B)

Federal regulations mandate that IRBs require additional safeguards before approving research involving pregnant women, human fetuses, or in vitro fertilization.

An IRB may approve research involving pregnant women or fetuses if 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 other means.

If the research holds out the prospect of direct benefit solely to the fetus, then both the pregnant woman and the father must give informed consent unless he is unavailable, incompetent, temporarily incapacitated, or the pregnancy resulted from rape or incest.

In general, neonates of uncertain viability may be involved in research if 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 if 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. In either case, the consent of either parent is required.

In general, nonviable neonates may be involved in research if the vital functions of the neonate will not be artificially maintained, the research will not terminate the heartbeat or respiration of the neonate, there is no added risk to the neonate from the research, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means. Consent of both parents is generally required.

No inducements, monetary or otherwise, may be offered to terminate a pregnancy.

Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy. Individuals engaged in the research will have no part in determining the viability of a neonate.

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by an in accord with the requirements of 45 CFR 46 subparts A and D.

Research involving human fetal tissue (placenta, or tissue from a spontaneous or induced abortion or from a still birth) is evaluated as tissue specimen research, using the guidelines for research involving specimens.

Studies using human embryos involve very explicit regulations concerning consent and study procedures. Refer to Texas and UNTHSC embryonic stem cell research policy (see Section 13.4).

12.3 Prisoners in Research (45 CFR 46 Subpart C)

Section updated on 08/12/14 related to the definition of “prisoners”; policy change in prisoner definition received approval by the convened IRB on May 7, 2013, effective immediately.

Prior to initiating Office of Research Compliance review, investigators should obtain written indication (in the form of a letter) from the authorities at the prison/institution where they plan to conduct the research. This letter should provide clear authorization for researcher access to the location and/or subjects (prisoners). Receipt of this written indication of authorization will be required before IRB review can commence. Please Note: In some cases it is appropriate for the written indication to be contingent on IRB review and approval of the research. Please consult with Office of Research Compliance prior to initiating any studies involving prisoners.

Definition and Guidance regarding Prisoner and Prisoner Representative

Prisoner (federal definition): Any individual involuntarily confined or detained in a penal institution. The term is intended to include 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 (45 CFR 46.303 (c)). This includes situations where a research subject becomes a prisoner after the research has started.

Individuals are prisoners if they are in any kind of penal institution, such as prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

Common examples of the application of the regulatory definition of prisoners are as follows:

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration are prisoners;

however, individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.

- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration are prisoners; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to nonpenal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
- Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
- Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind frequently require an analysis of the particular circumstances of the planned subject population. Institutions may consult with OHRP when questions arise about research involving these populations.

Prisoner Representative: Any individual who can represent the concerns that prisoners might have about research, who has a working knowledge of prison conditions and the life of prisoners. Suitable persons would include former prisoners, prisoner chaplains, or social workers who deal with prisoners or the families of prisoners. A prisoner legal advocate is also acceptable.

Definition of Risk under Subpart C

The definition of minimal risk under Subpart C is defined as 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.” This differs from the definition in Subpart A because it specifically describes harms as “physical or psychological.” However, the IRB will also evaluate a wider range of risks including social, legal, and economic when reviewing prisoner research at UNTHSC.

Secondly, Subpart C states that the risk of harm must be relative to the “daily lives” of “healthy persons.” Prisoners may be exposed to significant risks in their “daily lives.” For this reason, the IRB will consider “daily life” to be based on the lives of healthy persons who are not incarcerated.

Overview

Because incarceration affects a person's ability to make a truly voluntary decision whether or not to participate in a research project, the federal regulations provide additional safeguards for the protection of prisoners.

Studies that recruit prisoners will need to be reviewed at a fully-convened IRB meeting with a prisoner representative present for the discussion and vote of that study protocol.

Thus, prisoner research CANNOT be reviewed and approved at an Exempt or Expedited review level.

If a study was not initially approved to recruit prisoners, the investigator may not enroll prisoners (e.g., a prisoner who is brought to UNTHSC or one of its affiliates for treatment and happens to be eligible for a research study, may not be enrolled in a study unless that study was reviewed and approved to include prisoners, and a prisoner representative was present during the discussion and vote on the study).

The prisoner rules also apply to a subject who, at a later date, becomes a prisoner because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration; an exception is when the protocol specifically states that such a transitioning subject (to prisoner status) will be discontinued from further participation. Where the protocol does not specify what happens when a subject becomes a prisoner, as defined by these principles and procedures, two options are available to the investigator.

- If an investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or
- an amendment must be submitted requesting review for the inclusion of prisoners as subjects. With the exception of special circumstances, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all the requirements of Subpart C have been satisfied with respect to the relevant protocol.

The federal Office for Human Research Protections (OHRP) has allowed in special circumstances, in which the Principal Investigator (PI) asserts that it is in the best interest of the subject to remain in the research study while incarcerated; the IRB Chair may determine that the subject can continue to participate in the research until the requirements of Subpart C are satisfied.

Additional Considerations for Prisoner Subjects

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that 45 CFR 46.305:

1. The research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);
2. Any possible advantages accruing to the prisoner through their 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 their ability to weigh the risks of the research against the

value of such advantages in the limited choice environment of the prison is impaired;

3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
5. The consent information is presented in language which is understandable to the subject population;
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on their parole; and
7. Where the IRB finds there may be a need for follow-up examination or care of subjects 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. Subjects must be adequately informed of this fact.

If the research is conducted or supported by HHS, the University must certify to the HHS Secretary (through OHRP) that the IRB has approved the research under the HHS regulations for research that involves prisoners as participants, and the HHS Secretary must determine that the research meets one of the approvable categories.

Research Involving Prisoners Is Never Exempted

Four categories of research involving prisoners are permitted under the federal regulations (46.306).

Research that is not greater than minimal risk may be allowable if it consists solely of the following:

1. Studies 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;
1. Studies 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;

Other research that may be allowable under federal regulations if it consists solely of the following includes:

1. 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 of HHS (through OHRP) has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of their intent to approve such research; or definition of “minimal risk” is different from the definition in 45 CFR 46.102(i)]
2. 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 (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his/her intent to approve such research;

Research in the first two categories is not likely to benefit the subject directly. Therefore, it must present no more than minimal risk. Research in the third and forth categories are more likely to directly benefit the subject.

The Informed Consent form must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on their duration of incarceration or terms of parole. The IRB must determine whether assent is a requirement for research pertaining to prisoners that are children.

Waivers for Epidemiological Research Involving Prisoners

On June 20, 2003, new DHHS regulations were put into place stipulating that some epidemiological research conducted by DHHS involving prisoners may be eligible for a waiver. This allows prisoners to participate in epidemiological research that focuses on a particular condition or disease that might affect prisoners, as it could members of the general population.

Prisoners Who Are Minors

The UNTHSC IRB adheres to the federal and state regulations when reviewing human subject research that involves the use of juvenile offenders as subjects. When reviewing the research, the Board will also consider Subpart D (Additional Protections for Children Involved as Subjects in Research) in addition to 45 CFR 46 and Subpart C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects).

Juveniles under the age of 18 who are tried as adults will be considered adult prisoners. Therefore, they can consent to participate in a research study without parental permission. However, if they are released from prison prior to the age of 18, they will return to their minor status. At this time, parental permission for the subject to continue participating in the research study would be required.

12.4 Cognitively-Impaired Persons

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional HHS regulations specifically govern research involving persons who are cognitively impaired. While limited decision-making capacity should not always prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population. Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur during situations associated with high levels of stress (e.g. death of a family member). Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally-impaired. Some research questions may be answered only by research that involves persons with impaired decision-making capacity. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. Limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual subject but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non-therapeutic approaches may benefit subsequent generations.

OPHS and the IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons:

1. Research not involving greater than minimal risk;
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
3. The risk is justified by the anticipated benefit to the subjects;
4. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
5. Adequate provisions are made for soliciting the assent of the subject and permission of their legally authorized representative.

The IRB uses the following criteria for reviewing studies that involve Cognitively-Impaired Persons when the research is greater than minimal risk, there is no prospect

of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition:

1. The risk represents a minor increase over minimal risk;
2. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. Adequate provisions are made for soliciting assent of the subject and permission of their legally authorized representative.

Protecting Cognitively-Impaired Subjects:

The National Institutes of Health (NIH) offers the following points to consider, assisting IRBs and investigators in biomedical and behavioral research in their effort to protect subjects in research who are, may be, or may become decisionally-impaired. In any case, seek guidance from OPHS and or UNTHSC general counsel on this topic.

Conflicting Roles and the "Therapeutic Misconception"

Potential and actual research subjects, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic and possibly creating confusion among subjects and their families.

Assessing Capacity to Consent

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in subjects' decision-making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision-making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally-impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation.

Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent. Both IRBs and investigators must keep in mind that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Because no generally accepted criteria for determining capacity to consent to participate in research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The investigator should propose some means to demonstrate to the IRB how subjects will be evaluated for a capacity to provide informed consent. In some cases, the investigator may have to rely upon a legally-appointed guardian or caregiver to provide consent for such incapacitated subjects. Consenting on behalf of a subject must be a process and approach reviewed and approved by the IRB.

Medical Experimentation Involving Cognitively-Impaired Individuals

Individuals are considered competent unless proven otherwise. If a potential subject is found to be incapable, the federal regulations allow a “Legally Authorized Representative” to consent on their behalf.

Cognitively-Impaired in Non-Emergency Room Environments

The research covered is that of medical experiments that “relate to the cognitive impairment, lack of capacity, or serious life-threatening diseases and conditions of research subjects.” If a person is unable to consent and does not express dissent or resistance to participation in such research, surrogate informed consent may be obtained from a surrogate decision-maker with reasonable knowledge of the subject. The proxy decision maker is to use a “substituted judgment” standard if possible; if not, a “best interests” standard. The proxy shall include any of the following persons, in the following descending order of priority:

- The person's agent pursuant to an advance health care directive;
- The conservator or guardian of the person having the authority to make health care decisions for the person;
- The spouse of the person;
- An individual as defined as “domestic partner”;
- An adult son or daughter of the person;
- A custodial parent of the person;
- Any adult brother or sister of the person;

- Any adult grandchild of the person;
- An available adult relative with the closest degree of kinship to the person.

When there are two or more available persons who may give surrogate informed consent and who are in the same order of priority, if any of those persons objects to have the subject participate in the medical experiment, consent shall not be considered as having been given. Also, consent of a person who is in lower priority cannot supersede the refusal to consent by a person who is a higher priority surrogate.

Cognitively-Impaired in Emergency Room Environments

Surrogate informed consent may be obtained from a surrogate decision maker who is any of the following persons:

- The person's agent pursuant to an advance health care directive;
- The conservator or guardian of the person having the authority to make health care decisions for the person;
- The spouse of the person;
- An individual defined as a “domestic partner”;
- An adult son or daughter of the person;
- A custodial parent of the person;
- Any adult brother or sister of the person.

When there are two or more available persons described in the above list, refusal to consent by one person shall not be superseded by any other of those persons. Note that the rules on proxy consent do not apply to subjects who lack capacity to give informed consent and are involuntarily committed, voluntarily admitted, or admitted on conservator-request to a psychiatric hospital.

Investigators should consult the IRB for guidance when the potential subjects are in one of the above categories.

Determination of Subjects' Capacity to Consent

The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator that is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator that can best make a

judgment of the subject's ability to understand and follow the protocol. In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject actually enrolls.

The American Journal of Psychiatry, 155:11, November 1998, published "Guidelines for Assessing the Decision-Making Capacities of Potential Research Subjects with Cognitive Impairment." Investigators are encouraged to review this article.

The National Bioethics Advisory Commission's report, published December 1998, "Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity" should also be reviewed.

Voluntariness, Consent, and Assent

Closely related to the determination of the ability to comprehend the nature of the study is the importance of ensuring that subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.

In conclusion, varied degrees of research risk and decisional impairment call for varied levels of scrutiny and safeguards; additional protections may be necessary in certain circumstances. Treating all individuals who have cognitive deficits as capable, at times, of understanding research is respectful of their autonomy. It also exemplifies the principle of "respect for persons" in The Belmont Report. Many individuals, adequately informed, may be willing to undertake certain risks so that they, or others, may benefit in the future. Researchers and IRBs must strive for a balance that maximizes potential benefits and opportunities, recognizes and extends individual autonomy, and minimizes risks associated with scientific inquiry.

Chapter 13: Specialized Research

CHAPTER CONTENTS

- Chart Reviews
- Genetic Research
- Human Gene Transfer Research (“Gene Therapy”)
- Stem Cell Research
- Institutional Research
- Secondary Data Analysis
- Specimens (Human Biological Materials)
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- International Research

Overview

This chapter discusses various other types of studies that researchers may conduct and provides an explanation of unique requirements and steps needed to conduct compliant human subject research. A list of types of studies follows but the list is not exhaustive. Studies that provide unusual approaches or novel situations should be discussed with the IRB before submission.

13.1 Chart Reviews

A human subject is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable “private information”. When patients have the expectation that their information is privileged, and when researchers look at more than one

record to analyze for generalizable information, this becomes human subjects research. Therefore, medical or other chart/record review research requires IRB review and approval because of the private nature of the contents.

The IRB Chair may authorize a waiver of informed consent for chart review research studies if the study is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation. Generally, a waiver of consent is granted when all of the chart information that will be used in the research study exists in the medical record prior to the date of the IRB application.

Investigators should include the appropriate form requesting this with their IRB application for a chart review (see Appendix C for list of forms).

If some or all of the chart information that will be used is from medical appointments or hospitalization that will occur in the future (e.g., after the date of IRB approval), then consent from those subjects may be required. In order to assist the IRB in making the determination for waiver of consent, the investigator should provide the inclusive dates of medical record information that will be used in the study. This can be noted in the appropriate place on the IRB application and in the protocol synopsis.

The IRB may also waive the requirement for a Health Insurance Portability and Accountability Act (HIPAA) Authorization if the following criteria are met:

The use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals, based on, at least, the presence of all of the following elements:

1. An adequate plan to protect the identifiers from improper use and disclosure;
2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
3. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
4. The alteration or waiver will not adversely affect the privacy rights and the welfare of the individuals;
5. The research could not practicably be conducted without the alteration or waiver or alteration; and
6. The research could not practicably be conducted without access to and use of the protected health information.

In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the investigator should provide the IRB with a list of specific variables that will be used from the medical record chart. This could be done in the application itself, or by including the data collection forms that will be used for compiling the chart information.

For additional information, refer to Chart 5 of the Human Subject Regulations Decision Charts (see Appendix E). Also visit the chapter on HIPAA regulations and requirements associated with research (Chapter 16 “Health Insurance Portability and Accountability Act”)

13.2 Genetic Research

Genetic information is uniquely personal information and has the potential to influence employment, insurance, finance, education, family relationships and possibly self perception. Therefore, genetic information collected for a study, must be carefully maintained in order to protect against stigmatization, discrimination, or significant psychological harm to the subject or the subject’s family. The following should be addressed by the PI in the IRB Application and protocol and reflected in the Consent Form:

- Discuss information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study;
- Discuss identifying information available to other researchers if their sample and/or associated data are part of a registry or database;
- Discuss the extent of subject and sample confidentiality if the sample and subsequent information will be part of a registry or database;
- Discuss the rights and limitations of subjects to require destruction of their sample and/or associated data at a future date;
- Discuss the rights of subjects to require that their sample and or associated data be stripped of any identifying information, and limitations on such rights of subjects;
- Discuss mechanisms for maintaining confidentiality in long-term studies, registries, or databases;
- Discuss the availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on);
- Discuss potential for commercial profit by the institution, investigator or sponsor from information gathered in this study;
- A clear statement that the sample/data, any cell lines, profits from data etc., are the property of the University and/or the study sponsor;

- Discuss if genetic information will be disclosed to the subject or another party, the investigator disclosing the information must be named and the specific genetic information being disclosed must be stated;
- Discuss information to be disclosed in a manner consistent with the recipient's level of knowledge, e.g., information would be phrased differently when disclosed to a lay person versus a physician.

Before involving minors in DNA research, the parent(s) or legal guardian(s) must review and sign the Parental Permission Form/HIPAA Authorization. The Parental Permission form must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them.

Whenever appropriate, the minor's assent should be solicited. Upon reaching the age of majority, if the subject requests that their information be disclosed, that fact should be included in the Adolescent Assent Form. Investigators must follow the appropriate measures with regard to releasing such information (e.g., counseling, etc.).

In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed unless otherwise required by law or as a direct component of the research project and hypothesis.

Investigators are encouraged to contact OPHS staff for suggested language for genetic research and for storing tissue or specimens for future use.

Collection of Third-Party Information in Research

To generate data relevant to a specific genetics or clinical care research questions, it may be necessary to collect information about (unenrolled) relatives of an enrolled subject. Common items in a family or family history typically include age, gender, health information, and the relationship (e.g. sister, nephew) of each unenrolled person to the enrolled subject (in the context of pedigree research the original subject is referred to as the “proband”). The analysis of family or “third-party” information is often critical to determine a potential mode of inheritance, penetrance, expressivity, and the range and severity of a disorder or expectation of familial disease onset. Some studies also require family information to map and identify genes. The unenrolled individuals about whom such information is collected to generate the pedigree or understand clinical relationships are often referred to as “third party subjects”.

Risks: Clinical Care vs. Research:

By their nature, genetic assessments directly or indirectly include information about the relatives of the person being studied. It is important to distinguish between the clinical and research contexts for including such information in analysis. In many cases, family information is needed to diagnose an individual, as part of a diagnostic and therapeutic

assessment, not as part of a research study. Thus, it is important to recognize the difference between collecting this information in order to confirm a diagnosis in an individual seeking clinical care and collecting this information for the purposes of research.

In context of research, it is possible that participation in some genetics studies may alter (positively or negatively) family relationships (e.g. genetic breast cancer studies in families). Even the solicitation of research participation within extended families may expose differences among relatives in attitudes or beliefs, which may cause problems in the family. When individual research findings are returned to subjects, there is a potential to differentiate, or sort, relatives based on their “at risk” status, disease status, or reproductive risks and this can potentially create undesirable changes in family dynamics.

Further, genetics research may raise issues stemming from the discovery of misidentified relationships, such as misattributed paternity or unknown adoption. These types of risks may also affect family members who are not subjects in the research*. Therefore, the IRB should consider how to handle situations in which close family members (e.g. parents of adult children or identical twins) choose not to participate in the research. The IRB should ensure that any reasonably foreseeable psychological or social harm to which the research subject may be exposed is explained during the consent process.

Depending on the nature of the information collected, third-party individuals may be affected by the research. An important issue for investigators and IRBs is determining when the information that is collected requires that a “third-party” be classified as a human research subject, in accordance with 45 part 46 of the Federal Policy. This is a controversial and unsettled area of human subjects’ protection for research in general, and genetics research in particular. Until clear guidance is available, investigators and IRBs will use their best judgment in determining when information on such “third parties” is both identifiable and private, when third parties must be consented, and when a waiver of consent for a Third Party would be appropriate. When third-party issues are discussed and solved by the IRB, it is essential that the meeting minutes reflect this discussion.

*Several organizations have developed policy statements to address an investigator’s “duty to warn” family members about genetic information that may have direct implications for their health, including the American Society of Human Genetics, the Ethical, Legal and Social Implications (ELSI) Task Force on Genetic Testing, and others.

13.3 Human Gene Transfer Research (“Gene Therapy”)

All protocols involving the deliberate transfer of recombinant DNA (Deoxyribonucleic nucleic acid), or RNA (Ribonucleic acid) derived from recombinant DNA (human gene transfer) have additional reviewing, reporting, and consent form requirements. Please see the following requirements as outlined in the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

Human gene transfer, often called “gene therapy,” refers to the process of transferring specially engineered genetic material (recombinant DNA or RNA derived from recombinant

DNA) into a person. To avoid the misconception that this technology is therapeutic, the term “human gene transfer research” is preferred to “gene therapy.”

Two agencies, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), provide special oversight of human gene transfer research at the federal level. Locally, human gene transfer research is reviewed by the UNTHSC Institutional Biosafety Committees (IBCs) in addition to Institutional Review Boards (IRBs). Special review and safety reporting requirements highlight the importance of communication and information sharing between these bodies.

FDA

The FDA’s role is to determine whether or not a sponsor may begin studying a gene transfer product and, ultimately, whether it is safe and effective for human use. This process of review and authorization of gene transfer research is conducted by FDA’s Center for Biologics Evaluation and Research (CBER). Sponsors of gene transfer products must test their products extensively and meet FDA requirements for safety, purity, and potency before they can be administered to humans or sold in the United States.

When a manufacturer is ready to study the gene transfer product in humans, it must obtain an investigational new drug application or IND. In the IND, the manufacturer explains how it intends to conduct the study, what possible risks may be involved and what steps it will take to protect subjects, and provides data in support of the study 21 CFR 312.23.

NIH

The NIH is the major public funding agency for biomedical research, supporting, among many other lines of scientific investigation, much laboratory and clinical research on vectors, disease models, and human applications of gene transfer technologies. In carrying out this function, the agency assumes stewardship and oversight responsibilities for promoting the safe and responsible conduct of this research. With respect to human gene transfer research, NIH’s primary role in this field is to evaluate scientific, safety, and ethical aspects of human gene transfer research and communicate its findings to the scientific community, IRBs and IBCs, and the public.

The NIH Guidelines articulate standards for investigators and institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived from recombinant DNA. These guidelines outline requirements for institutional oversight. Appendix M of the NIH Guidelines describes points to consider in the design and submission of human gene transfer trials, including the registration of protocols with NIH, the review procedures of the Recombinant DNA Advisory Committee (RAC), the conduct of informed consent, and annual and expedited reporting requirements. Institutions that receive NIH funding for basic and clinical recombinant DNA research must assure to NIH that all research conducted at or sponsored by the Institution complies with NIH Guidelines.

Investigators have an ongoing responsibility to monitor human gene transfer trials and to keep the NIH Office of Biotechnology Activities (OBA), as well as IRBs, IBCs, FDA, and any sponsoring NIH institutes or centers, informed of any adverse events that occur in a trial. If a serious adverse event occurs that is unexpected and could be possibly associated with the gene transfer product, a sponsor is required by regulation to notify FDA within 15 days of the event, and investigators should notify OBA of the problem within 15 days of their notification to the sponsor. Serious adverse events that are fatal or life threatening must be reported within seven days. If warranted by the nature of these events, the FDA may mandate changes to the human study and require more preclinical studies, put the clinical study on hold, or stop the study altogether.

The NIH and FDA have developed a national database for gene transfer clinical research, the Genetic Modification Clinical Research Information System (GeMCRIS) to enable systematic analysis of data across all human gene transfer trials and to enhance communication and application of knowledge gained from the studies. The system provides a standardized means for reporting, organizing, and analyzing data related to adverse events in a format accepted by both the NIH and FDA.

Potential risks of gene transfer studies include those associated with the study procedures as well as risks of harm associated with the study agent. In some cases, the potential risks associated with gene transfer may weigh against the involvement of human subjects in such trials. The IRB need to consider the risks and benefits of a human gene transfer study carefully, and, if a protocol is approved, ensure that participants will be thoroughly informed of the risks and benefits involved in the procedure.

Because gene transfer is innovative and its long-term risks are not well understood, the NIH Guidelines require investigators to inform prospective participants that they will be asked to participate in long-term follow-up that extends beyond the active phase of the study. Investigators need to explain the rationale for long-term follow-up, the specific follow-up activities planned, how long follow-up will continue, and what, if any, procedures participants will be asked to undergo. As with any research covered by the Federal Policy, participants have the right to withdraw from the study at any time, including during follow-up.

The NIH Guidelines state that investigators should inform subjects that an autopsy will be requested at the time of death, no matter what the cause, to obtain vital information about the safety and efficacy of gene transfer. Subjects should be asked to advise their families of the request and of its scientific and medical importance. During the informed consent process, the investigator should explain that the subject is not being asked at this time to consent to autopsy, nor is it required for study participation. However, subjects should be encouraged to express their wishes about an autopsy to their families so that family members are prepared to consider it at the time of the subject's death.

The NIH Guidelines require that investigators describe in the protocol any potential benefits and hazards of the proposed gene transfer to persons other than the human subjects receiving the experimental intervention. Specifically, investigators must address whether there is a significant possibility that the inserted DNA will spread from the human subject to other

persons or to the environment and what measures will be undertaken to mitigate any public health risks. The IBC should be involved in assessment of community health risks.

IBC (Institutional Biosafety Committee)

An IBC is a review body responsible for ensuring that basic and clinical recombinant DNA research is conducted safely and in accordance with NIH Guidelines. The IBC must review and approve all experiments involving the deliberate transfer of recombinant DNA, or RNA derived from recombinant DNA, into any human research participants.

13.4 Stem Cell Research

UNTHSC follows current federal regulations regarding stem cell research. Investigators are encouraged to consult with OPHS well ahead of time, and allow sufficient time for IRB review when submitting IRB applications that involve stem cell research. For more information, please refer to the following websites:

Federal Policy: <http://stemcells.nih.gov/policy/>

National Institutes of Health Guidelines on Human Stem Cell Research:
<http://stemcells.nih.gov/policy/2009guidelines.htm>

Executive Order 13505-Removing Barriers to Responsible Scientific Research Involving Human Stem Cells: <http://edocket.access.gpo.gov/2009/pdf/E9-5441.pdf>

Congressional Legislation (House and Senate bills relating to stem cell research):
<http://stemcells.nih.gov/policy/legislation.asp>

13.5 Institutional Research

Institutional research involves data collection, analysis, or reporting about educational, administrative, or other aspects of a college or university for either institutional self-improvement or external reporting. In most universities, institutional research performs such issues as enrollment management; program evaluation; student outcomes assessment; space planning and utilization; financial analysis; and faculty or staff planning. Data most often include institutional databases, surveys, focus groups, interviews, tests, work samples, and archival materials. Institutional research is specific and applied. It is not intended to generate theory, provide results that will be generalized beyond UNTHSC, or advance knowledge. It is intended to be of direct, practical value.

While the term “institutional research” is most often used in an academic setting, the function is found in a wide array of educational, service, and other organizations. For example, many health care providers and service organizations have offices of Quality Assurance, Organizational Effectiveness, Planning and Assessment, or Evaluation.

To what extent does institutional research fall under the regulations governing IRB review? The main issue is the extent to which institutional research fits the federal definition of “research” used in IRB regulations. To our knowledge, there is no definitive guidance about this, and institutional researchers engage in a wide range of practices. The OPHS is charged with reviewing all research proposals using human subjects which are conducted by the faculty, staff, graduate or undergraduate students. OPHS, and where appropriate, IRB review is an ethical and legal obligation. Federal regulations provide guidance about the responsibilities in this regard.

UNTHSC strongly encourages managers to build a strong empirical foundation for their decisions and plans, and to evaluate the effectiveness of their programs. Institutional research is vital in this regard. At the same time, it is essential that we comply with OPHS and IRB principles and procedures and regulations. In seeking the proper balance, we propose the following approach.

Institutional research that is conducted for internal use only and to inform management practice and decision-making, falls outside the federal definition 45 CFR 46 of “research” and hence does not need to undergo review by the OPHS and the IRB.

If data collected during institutional research becomes “research data”, or if it is collected to be “research data” (by contributing to generalizable knowledge through publication, change in intent, or the activity is mixed human subjects research/non-human subjects research), the IRB must review and approve the research, prior to the use of, or the collection of the data, for research purposes.

13.6 Secondary Data Analysis

Any research that involves secondary use of data where individual subject records are involved requires OPHS review. For example, an investigator who plans to analyze an existing data set obtained from another source should submit an application for OPHS review if the data set contains records on individual human subjects. If the data set contains no identifiers (either direct or linked code numbers), the project may qualify for Exempt category status and review. If the data set contains identifiers, and does not contain private information (information about behavior that occurred in a context in which the individual could reasonably expect that no observation was taking place or involved no information which had been provided for specific purposes for which the individual could reasonably expect would not be made public), the project might also qualify for Exempt category status and review. Otherwise, the project may be eligible for expedited review. The OPHS may waive informed consent if research is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

Secondary analysis of already aggregated data sets (e.g., meta-analysis) qualifies for Exempt category status and review.

Recall that in any case, all projects, even those involving secondary data analyses, must be submitted to OPHS for initial review, categorization and approval. The investigator is always encouraged to contact the OPHS for clarification.

For additional information, see Chart 5 of the Human Subject Regulations Decision Charts (See Appendix E).

13.7 Research Using Human Biological Materials (Samples)

The use of human biological materials (samples) in research requires review by OPHS and, where appropriate, the IRB. OPHS and the IRB's roles are to ensure that research using human samples is conducted in an ethical manner that protects the human subjects from whom the samples were obtained.

Research that utilizes human samples may qualify for Exempt, Expedited, or Full Board review, dependent upon the potential risks the research poses to subjects. This determination is one that must be made by OPHS, not by the investigator. Therefore, faculty and staff should consult with OPHS staff prior to conducting any research that involves human samples.

What is Considered Human Biological Material?

Human biological materials include tissue samples, blood, sputum, urine, bone marrow, and cell aspirates. Many researchers refer to these materials as “samples” or “tissues” in their IRB applications and research protocols. They will be referred to as “samples” throughout this section.

Categories of Samples

Existing Samples

Many research studies involve samples that are retrospective in nature. The archived samples were originally collected for medical/clinical purposes, or they were collected for the establishment of a research tissue repository. These will be referred to as “existing samples.” Existing samples may be frozen at the time of collection or preserved in some other manner that allows storage at room temperature for long periods of time, such as paraffin blocks or histologic slide files.

Prospective Samples

Research using human samples may also be prospective in nature, using freshly obtained samples from the human subjects enrolled in the research study. These types of samples will be referred to as “prospective samples.”

Unidentified Samples

Unidentified samples may also be referred to as “anonymous” samples. Unidentified samples are collected without direct identifiers. Therefore, personal information was not collected and cannot be retrieved by the investigator or repository. These types of samples involve the lowest level of risk.

Unlinked Samples

Unlinked samples were originally collected with identifiers, however these samples have been “stripped” of these identifiers. Therefore, identifying a person through the demographic or health data associated with the unlinked sample would be very difficult. Unlinked samples may have been stripped of identifiers prior to being received by the investigator or institution. Samples may also become “unlinked” after they are in the possession of the investigator/institution when they are stripped of identifiers by a disinterested (third) party. Unlinked samples may also be referred to as “anonymized” samples.

Identifiable Samples

Identifiable samples are those in which the identity of the person providing the sample can be easily discovered. The federal government considers samples to be identifiable when the sample or related health information/data can be linked to a specific person by the investigator, either directly (name, social security number, or medical record number) or through a unique study identification number, sometimes referred to as a “code.”

Coded Samples

“Coded” samples, often called “linked” samples, are those in which the identifier(s) have been replaced with an identification number or numerical code, and a master list or key that provides a link between the unique identification number and specific person exists. Coded samples are considered to be identifiable samples because they contain a link to the individual.

Evaluating the Level of Risk

The major risk to subjects in research that involves human samples is informational risk (i.e. breach in confidentiality). This level of risk will vary depending upon if the samples are unidentified or identifiable. Research with unidentified samples presents the lowest level of informational risk, and should qualify for Exempt review. Research with unlinked samples is also considered to be low risk, and may qualify for Exempt review as well.

Research with identifiable samples and coded samples will present a greater informational risk to subjects because there is a potential risk of disclosure of demographic or protected health information. This information may be harmful to the subject if it falls into the wrong hands. Potential harms to the subject from a breach in confidentiality include the loss of health insurance or life insurance, loss of employment, or social stigmatization, among others.

When designing a protocol that involves research with samples, investigators should focus on creating an appropriate plan to reduce this informational risk. OPHS recommends that investigators create a section in the protocol titled “Special Precautions.” In this section, investigators should provide a detailed description of how the specimens and related health information will be “stripped” of identifiers, and describe an appropriate sample/data storage and security plan. Another important aspect of evaluating risk in research that uses coded samples is the security of the master list or code key, and the policies that determine when the master list or code key can be accessed or broken. Detail on this should be provided in the protocol synopsis (if applicable) for identifiable samples that are collected at UNTHSC or at outside entities.

Per federal guidelines, research with coded samples may qualify for Exempt review if:

1. The specimens were not collected specifically for the proposed research project described in the IRB application; and
2. If the investigator cannot easily determine who the specimen or related health information belongs to.

This situation may occur if the master list or key to the code was destroyed prior to the submission of the IRB application to OPHS. Additionally, investigators may enter into an agreement with the entity or individual who holds the master list/key that prohibits releasing it to the investigator under any circumstances or until the individuals are no longer living. Investigators who wish to use this option must submit an appropriate plan with documentation of the agreement to OPHS with the IRB application. Consult with OPHS staff for additional guidance on this topic.

Another important consideration in evaluating risk will be the nature of the study. Studies that examine germline cells, which contain inherited material from eggs and sperm that are passed to offspring, represent the greatest amount of risk because they relate to the inherited potential of the individual, which can have direct implications for current and future generations as well as racial/ethnic groups. Studies that examine typical (somatic) cells in the human body (internal organs, hair, skin, eyes, bones, blood, and connective tissue) are generally considered to be lower risk because they should not have direct implications for current and future generations.

Informed Consent to Use Specimens for Research Purposes

Human subjects protection regulations apply to the use of human samples in research studies. Therefore, to be in compliance with federal regulations, informed consent should be obtained from the subject prior to using his or her samples for research purposes (see Section 9.2 on the General Requirements of Informed Consent).

There are several types of research involving specimens, and each has its own set of regulatory, ethical and practical aspects and features:

- Retrospective Specimen analyses – in which samples have already been obtained for either clinical (non-research) purposes, or through an IRB-approved research collection protocol. These samples would constitute an “existing” sample collection. Note that in some cases, a project may involve both existing and ongoing (prospective) samples.
- Prospective Sampling – in which samples are being collected through an existing IRB-approved protocol, or will be collected for clinical (non-research purposes)
- Specimen Repositories (also know as Tissue-Sample Banks) – which may have also have data (medical, behavioral, demographic, etc.) associated with specimens

Research Involving the Use of Existing Specimens (Retrospective Specimen Studies)

In these studies, the samples already exist, having been collected for non-research purposes (via clinical care) or through a previous IRB-approved study.

It is important to consider that patients may give their permission for their samples to be used for research purposes when they consent to a medical procedure, or when they are admitted to a hospital or treatment center. OPHS recommends that investigators review medical intake forms at the entity where the samples were obtained prior to contacting OPHS for guidance on preparing their IRB application. OPHS staff will need to know this information before they can appropriately advise the investigator on how to proceed. Additionally, investigators will be required to submit a copy of the clinical document, such as a clinical consent form, indicating patient consent for their samples (and related data) to be used for research purposes. Again, a copy of these clinical consent documents should be submitted to OPHS along with the IRB application.

Waiver of Informed Consent

DHHS regulations permit the IRB to consider waiver of informed consent in research that involves samples for which informed consent was not obtained if the research meets the required criteria for Waiver of Informed Consent (see Section 9.7). The OPHS/IRB will evaluate the following when an investigator requests that informed consent be waived:

1. Wishes of the subject (personal autonomy);
2. The type of consent given for the tissue storage in the repository;
3. If the data associated with the sample will be secure and confidential after it is released to the researcher from the repository.

Additionally, HIPAA permits the use of unidentifiable samples collected prior to April 14, 2003 without informed consent in some situations (contact OPHS staff for guidance). Current FDA regulations do not permit any waivers of informed consent.

Investigators should submit the appropriate waiver form (see Appendix C) with their IRB application when requesting a waiver of informed consent. *Please Note:* To facilitate review, please make sure to initial, provide an appropriate explanation, and sign the form. Failure to complete the form appropriately may lead to a delay in the review/approval process for the IRB Application.

Research Involving the Prospective Collection of Specimens

Studies that involve the prospective collection of human samples will not be eligible for Exempt review. Therefore, investigators will need to submit an Expedited or Full Board IRB application to OPHS. Investigators should contact OPHS staff for guidance in determining the type of application that will be required when they are developing their protocol.

Per federal regulations, some research that involves samples may be eligible for Expedited review. This includes research that involves the collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, and research that involves the prospective collection of biological specimens for research purposes by noninvasive means (refer to Section 5.13 for specific detail).

In prospective studies, the collection of the sample may be solely for the purpose of the specific research project. The collection of the sample is (or is part of) the research intervention, which will typically occur at a research study visit.

However, in many prospective studies that involve samples, the collection occurs at a clinic visit or hospital stay rather than a study visit. Researchers may request permission to analyze the sample that is collected during the medical visit for research purposes. Subjects may also be asked to provide an additional sample (for example, “an extra vial of blood” or an “extra swab”) at their clinic or hospital visit for the research study. In these studies, clinicians and other medical personnel (such as physician assistants, nurses, and medical assistants) are often involved in the conduct of the research study by obtaining and transferring the sample to the investigator for analysis and storage.

A proper informed consent process will need to be in place for all prospective studies. The informed consent should clearly describe the process and procedures for the storage and future use of the human sample(s). The informed consent should also describe if identifiers linking the subject to the sample will be present, and if the subject can withdraw their sample from the study or repository in the future if they no longer wish to participate in the research (note that subjects whose samples will be unidentifiable will not be able to withdraw from the research in the future). All persons who are obtaining informed consent from subjects in prospective studies that involve samples should be listed as key personnel in the initial IRB application and protocol, or added using the “Application for Change in Study Personnel” form if they are added to the study after IRB approval. All key personnel are required to complete the appropriate educational training in the protection of human subjects, and submit a signed Conflict of Interest Form to OPHS if they are faculty, students, or employees of UNTHSC or UNT Health (see Section 8.2 for additional details on educational requirements).

Repositories

After collection, samples may be stored in specimen repositories or “tissue banks.” The repository may be small or may be very large with thousands or millions of samples. OPHS and the IRB are concerned with the following three types of repositories:

1. Repositories of samples collected prospectively for a research study or possible future research study;
2. Repositories of clinical samples that were collected during medical procedures, to be used in the future for diagnostic and/or predictive purposes; and
3. Banks of clinical samples for which there is excess tissue/material (beyond which is needed for future medical diagnosis) that may be accessed for research purposes.

Repositories that include samples that will be used in research studies should have an appropriate IRB approved plan in place to regulate the collection, storage, and distribution of samples. IRB review and oversight will be required for all such repositories that reside at UNTHSC (see additional detail below).

Banks of clinical samples not intended for research may not be subject to federal regulations or IRB review unless required the repository is federally funded or if IRB review is required by the institution. UNTHSC currently does not require IRB approval for banks of clinical specimens that are not intended for research purposes. However, HIPAA regulations will apply to the clinical samples stored in these repositories. In all cases, it is important to avoid the regulatory problem created by collecting samples in a clinical care enterprise that are actually intended for research purposes. If there is any expectation that samples may be used for research purposes in the future, it is best to establish that assumption at the beginning, and create a research specimen repository in compliance with federal regulations. Consult with OPHS staff for guidance on this topic.

Establishing Repositories at UNTHSC for future research use

Investigators who wish to create a repository of human samples that will be used for future research purposes will need to obtain IRB approval prior to establishing the repository. These Principal Investigators become “Repository Controllers” who establish and manage the collection, storage, access, and distribution of repository specimens. The IRB will review the operating procedures of the repository, including who will have access to the samples, coding of samples, and the process to ensure that future research projects are not conducted without prior IRB approval. Additionally, the IRB will consider ownership of the samples, privacy and confidentiality, process for withdrawing samples from the repository, plans for the transfer of samples to internal and external investigators, and oversight of future research involving the banked samples. The investigator may plan to use the banked samples for a variety of purposes. If so, this should be clearly described in the protocol synopsis.

Samples that will be prospectively obtained from subjects will require the informed consent of the subject before they can be placed in the repository. This consent should include the core elements described in the federal regulations at 45 CFR 46 (see Section 9.2). Additionally, it may be appropriate to provide an “opt in” and “opt out” option in the consent form that allows subjects to determine which types of entities/individuals may use their tissue for research (i.e. nonprofit, commercial, specific researcher) and for what purpose the samples may be used (i.e. cancer research, cardiovascular health research, gynecological research, etc). This is especially important for banked samples that will be used for a variety of research purposes. Existing samples that an investigator wishes to place in a repository may qualify for a Waiver of Informed Consent or they may require the consent of the subject (informed consent is described in the next section). Establishing a repository using donated and/or purchased samples is also discussed in greater detail later in this section.

It is important for investigators to remember that after the repository has been established, each individual research project that will utilize samples from the repository will require an individual IRB review and approval. Some of this research may qualify for Exempt review by OPHS. However, the individual(s) responsible for the oversight of the repository will need to ensure that access to the banked samples is only granted with IRB approval. Further, Repository Controllers (see above) should also be included as key personnel on the protocol to verify access and authorization for repository specimens and their associated data.

Additionally, in some circumstances, the IRB may require that a person whose sample is in the repository provide additional consent (i.e. be “re-consented”) to allow researchers to use their sample for their research. An example would be research that involves HIV testing of stored samples. This may involve re-contacting subjects to obtain their consent. Including an “opt in” and “opt out” clause in the consent form may reduce the need to re-contact subjects. Guidance on re-contacting subjects can be found on the OPHS website at:

<http://www.hsc.unt.edu/Sites/OPHS-IRB/Documents/ReContacting%20Guidance%20for%20Investigators.pdf>

Research using Existing Donated or Purchased Samples

Creating a Repository using Donated or Purchased Samples

Research studies at UNTHSC may involve the collection and analysis of existing samples and related health information donated by, or purchased from, an outside entity or individual. The investigator may wish to create a repository at UNTHSC that includes these donated samples and related health information. The related health information may be extensive in some situations (for example, an entire medical chart), and include a great deal of Protected Health Information (PHI). Investigators will be required to describe, in the protocol synopsis, to what extent the samples and related data will be de-identified before arriving at UNTHSC.

Additionally, investigators should also describe, again, in the protocol synopsis, the process in which identifiers will be “stripped” from the medical data. If the breadth of health information is extensive, the IRB will require that all identifiers be removed before the samples arrive at UNTHSC.

Ensuring Donated or Purchased Samples are Legally and Ethically Obtained

It is important that investigators ensure that the samples received from the outside entity were and continue to be legally and ethically obtained. Documentation describing how the samples were obtained should be submitted with the IRB application.. This may be demonstrated by obtaining a copy of IRB approval for the collection of samples from the outside entity. Please Note: A copy of the outside entity's IRB approval should be submitted to OPHS with the UNTHSC IRB application.

Ownership of Samples

Investigators should describe, in the protocol synopsis, who will own the samples and related data after they arrive at UNTHSC, and indicate if the outside entity/individual will retain any ownership or access to the samples after they are transferred to UNTHSC.

Transfer of Samples and Related Data to other UNTHSC Researchers

An investigator serving as the Repository Controller may wish to allow other UNTHSC researchers to use samples stored in a repository for future research purposes. In this case, a section titled "Transfer of Specimens and Data to UNTHSC Researchers" should be included in the protocol synopsis. This section should describe the process for how specimens and data will be transferred to other investigators at UNTHSC. As mentioned earlier, an entirely new IRB application will be required before an investigator can access these samples or data for their individual research project.

Transfer of Samples and Related Data to Outside Researchers

An investigator may wish to transfer samples to an outside researcher for several reasons. The outside researcher may be involved in the analysis of the samples and related data for a current research project the investigator is conducting, or for a collaborative research project conducted by both UNTHSC and an outside entity. Additionally, an investigator may wish to allow an outside researcher to use samples stored in a repository for a future research project that does not involve UNTHSC.

In all cases, an appropriate set of procedures will need to be in place to protect the subject's confidentiality during this transfer. Investigators are encouraged to consider such future arrangements and to establish these procedures within the initial protocol application. However, there may be situations when it is necessary to modify an existing IRB approved protocol to include this option. The protocol should include a section titled "Transfer of Specimens and Data to Non UNTHSC Researchers" that describes a detailed plan for the transfer of samples to outside researchers. To protect subject confidentiality, the protocol should describe how the samples and data will be labeled when they are transferred, and the process for "stripping" all identifiers from the data before they leave UNTHSC. The protocol should also list the outside researchers by name, and describe who will own the samples after they are received by the outside investigator if this information is available. OPHS understands that an investigator may not be able to name a specific outside researcher during

the initial IRB application process or request for modification to the protocol, however would like to include this option should there be a future need to transfer samples. It is appropriate to incorporate this option into the protocol. As mentioned above, the protocol should include a section titled “Transfer of Specimens and Data to Non UNTHSC Researchers” that describes an appropriate plan including how samples will be labeled and stripped of identifiers prior to transfer. Once the Principal Investigator (PI) has identified the outside entity who will receive and analyze the specimens, that PI is required to submit a request for approval to OPHS. This memorandum should name the outside entity, describe what the outside entity will do with the samples, describe who will own the samples after they are received by the outside entity, and how the samples and accompanying data will be securely maintained. The investigator should not send the samples and/or related data to the outside entity until they have received notice of approval in writing from the OPHS/IRB.

Subjects should be advised during the initial informed consent process that their samples and/or related data may be sent to an outside entity that is approved by UNTHSC for research purposes. Only subjects who consent to the transfer of specimens should have their samples and/or related data sent to outside researchers. In some cases, it may be necessary to re-contact and re-consent subjects who were advised that their samples and/or related data would not be transferred to outside researchers during the initial informed consent process. Investigators are encouraged to contact OPHS staff for guidance in this area. This will not be applicable for studies that qualify for a Waiver of Informed Consent.

Research Using Samples from Deceased Persons

Federal regulatory definitions of human subjects does not include deceased persons. Therefore, the use of samples obtained during an autopsy or the use of samples originally collected from a living individual who is now deceased is not considered research with human subjects. However, in most cases, other federal and state regulations may apply including HIPAA regulations. Investigators are encouraged to contact OPHS staff prior to initiating this type of research to ensure that appropriate HIPAA and/or IRB compliance is followed.

13.8 Biosafety Review and Approval and Human Subject Research

Institutional Requirement

Per institutional policy, an Institutional Biosafety Committee (IBC) protocol and Blood Borne Pathogen (BBP) training is required for all activities involving the use of human biological material including (but not limited to): blood and its components, body fluids, tissues and tissue fluids. This IBC protocol must receive review and approval by the Institutional Biosafety Committee.

It should be noted that the IBC is *not* part of the Institutional Review Board (IRB). While an IRB protocol focuses on the risk/benefit management of research from a human subject perspective, an IBC protocol focuses on the risk management of biological material from a biosafety perspective. Further, an IBC protocol is considered *separate* from the IRB protocol and IRB approval process. Therefore, researchers should *not* assume that

obtaining IRB approval satisfies this or other institutional requirements. Researchers are responsible for obtaining the appropriate approvals and clearance from all applicable offices, departments and regulatory agencies (e.g., Institutional Biosafety Committee, Office of Clinical Trials, Grants and Contracts, Research Conflict of Interest, Legal, Sponsor or funding agency and/or Marketing) *before* initiating a study in order to remain compliant with institutional policy, federal regulation and state law.

Effective February 1, 2017, IBC approval must precede IRB approval for any project involving human biospecimens. Any human subject protocol that involves unfixed biospecimens (saliva, serum, blood, buccal swabs, urine, unfixed tissue of any type, etc.) must have an IBC-approved protocol in order to be reviewed and approved by the IRB.

IRB Procedures and Guidance for Studies that Involve Human Biospecimens

For Existing, IRB-Approved Research Projects that Involve Human Biospecimens:

Investigators who already have such an IBC approval for their IRB-approved research project(s) should send a copy of the IBC approval letter to the Office of Research Compliance and indicate which IRB protocol(s) are linked to the IBC approval. It is the investigator's responsibility to provide clear and complete information indicating to which project(s) the IBC approval applies.

- During this transition period, investigators who do NOT have IBC approval for their IRB-approved research project(s) will have **until February 1, 2017** to obtain and submit to the Office of Research Compliance an IBC approval letter that is appropriately linked to their human research project(s).
- **If, by February 1, 2017 the Office of Research Compliance does not have IBC approval affiliated with a given IRB protocol involving human biospecimens, then that IRB protocol will be placed on Administrative Hold (Suspension) until an IBC approval is obtained and verified.**

When Submitting a New Research Project (that involves use of human biospecimens) for IRB Review:

- The investigator should include a copy of the IBC approval letter with the IRB protocol packet.
- If the investigator does NOT yet have an IBC approval letter, the IRB application will be placed on "hold" until the IBC approval letter is submitted and verified.

When Submitting an IRB-approved research project (that involves use of human biospecimens) for IRB Continuing Review:

- Investigators should submit a copy of the IBC approval letter to the Office of Research Compliance along with other documents associated with the Progress Report (or Final Report).
- If the project does not have IBC approval (or if the IBC approval period has expired), the IRB protocol will be placed on Administrative Hold (Suspended) until the IBC approval is made current. Investigators should avoid this “lapse” at all costs.

Note for Researchers

- (1) *IBC approval comes first.* Investigators do NOT need an approved IRB protocol in order to submit a Biosafety protocol. But, as a matter of institutional biosafety, investigators DO need to have documented Biosafety (IBC) approval in order to receive IRB approval to collect/conduct research involving human biospecimens.
- (2) *A single approved IBC protocol can be used for more than one IRB protocol.* The basis for IBC review and approval is to assure and document that the investigative team working with human biospecimens has appropriate staff training, facilities and inspection associated with the collection, storage and use of human biospecimens in research. Thus, a single IBC protocol can serve as evidence of biosafety approval for more than one project involving human subject research.

From the IRB’s point of view, a principal investigator may list a single Biosafety (IBC) protocol as relevant to any number of IRB protocols in that principal investigator’s name. Recall that an IBC protocol is evidence of appropriate safety precautions and training for relevant research staff. Thus, one IBC protocol for human biospecimens can be used for any number of IRB protocols coming from that lab/PI. The PI does not have to send in a separate IBC protocol for each IRB protocol. The key issue is for all activity covered by an IRB protocol involving human biospecimens to have appropriate Biosafety oversight and training for all listed personnel.

The Office of Research Compliance encourages investigators to require blood-borne pathogen (BBP) training for all personnel associated with their projects. Not only will this help facilitate a timely IBC protocol review and approval, but it is also good research and personal safety practice.

Other General Notes for Researchers

1. The IBC typically meets the third Wednesday of each month. Proper planning and documentation submitted for IBC review will facilitate a quick and effective review and approval. Investigators should not wait until the last minute to submit paperwork for IBC review.

2. The Institutional BioSafety Committee (IBC) approval of a protocol is valid for three (3) years. And like any other compliance committee approval, any and all changes to an approved protocol must be reviewed and approved by the respective committee(s) prior to implementation. Plan accordingly.
3. Investigators should maintain valid records with the Institutional Biosafety Committee (IBC): this includes updated Blood Borne Pathogen (BBP) training for personnel engaged in collecting or studying biospecimens, as well as IBC-required updates and notices.
4. When developing a biosafety plan, researchers should consider the following items:
 - Potential safety issues when collecting, managing, transferring and storing (short-term and long-term) of human biological material.
 - Precautionary measures for minimizing the potential risks associated with the collection, handling, transferring and storage (short-term and long-term) of human biological material.
 - Measures for maintenance, surveillance / monitoring and enforcing the safety protocol.
 - Education and training for those involved in the collection, handling and management of human biological material.
 - An emergency response plan in the event exposure to a hazardous agent or pathogen occurs.

Additional Information:

Submission of an IBC protocol is done through the Office of Environmental Health and Safety on-line submission and review (IDEATE) system. Here is a link for the information and website regarding IBC submissions:

<https://www.unthsc.edu/research/grant-and-contract-management/ideate-web-based-research-administration-system/>. That webpage contains links that will enable investigators to access an IDEATE tutorial and to enter the IDEATE portal to create an IBC protocol.

For *specific* guidance on developing an IBC protocol, investigators should contact the Bio Safety Officer, Maya Nair, PhD, at (817)735-5431 or by emailing the Biosafety Program Office (ibc@unthsc.edu).

Blood-Borne Pathogen (BBP) Training is available at the UNTHSC “INSITE” Training page: <https://insite.unthsc.edu/training/> Click on “Blood-Borne Pathogens”.

For more information about the required Blood Borne Pathogen (BBP) training program, investigators are advised to contact Dr. Janet Jowitt, Chief Nursing Officer at jan.jowitt@unthsc.edu, or by phone at (817) 735-2233.

13.9 Oral History Research

Recent guidance from the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection has stipulated that oral history, as the practice has been professionally defined, does not meet the regulatory definition of “research” and therefore is excluded entirely from full IRB review. However, like all research involving human subjects, oral history projects require prior review by UNTHSC OPHS. If an oral history project does meet the regulatory definition of research, it could still be “exempted” by OPHS, but that must be determined by the OPHS, not the investigator.

Simply talking with someone for background is not oral history. Oral history involves interviews for the record, explicitly intended for preservation as a historical document. Informed consent means that those being interviewed fully understand the purposes and potential uses of the interview, as well as their freedom not to answer some questions, and their identification in research and writing drawn from the interview. Legal releases are linked to issues of evidence and copyright. If a researcher makes explicit use of an interview in written work (both in direct quotation and paraphrase), the interview should be cited in a footnote so that others can identify and locate the information within the framework of extant evidence. Recorded interviews involve copyright, and interviewees must sign an agreement that establishes access for those who use the interview in any way. If the interviews are deposited in a library or archives, legal releases will establish ownership of the copyright and the terms of access and reproduction. If the interviews are published, legal releases will satisfy publishers’ concerns over copyright.

13.10 International Research

Procedures normally followed outside the United States for research involving human subjects may differ from those set forth in federal and University policies. These may result from differences in language, cultural and social history, and social mores. In addition, national policies such as the availability of national health insurance, philosophically different legal systems, and social policies may make U.S. forms and procedures inappropriate. Additional laws, regulations, and international directive may apply to research conducted in foreign countries, and may require further protections for research subjects. If protections are deemed equivalent, requests to review or waive some standard elements of U.S. approvals may be considered. However, protections afforded subjects must approximate those provided to subjects in the United States. The investigator is encouraged to contact the Director of OPHS to discuss these issues.

Investigators will be required to obtain a Research Ethics Review Board (IRB equivalent), also known as Independent Ethics Committees (IECs) approval for research done

internationally for studies that are more than minimal risk. Many universities outside of the United States have Ethics Committees that can review and approve the research. For studies that are minimal risk, the IRB equivalent to an approval letter or permission letter from the research site may be acceptable; however, it will be reviewed by OPHS and/or the IRB on a case-by-case basis.

International research studies must adhere to a recognized Ethics Codes such as: 45 CFR 46, the current version of the Declaration of Helsinki, and Council for International Organizations of Medical Sciences (CIOMS). Consent and recruitment documents must be in the language that is readable and understandable by the subjects or an approved translation method may be used. Additionally, the following issues should be discussed in the IRB application or be addressed in the IRB discussion:

- Benefits to subjects;
- Community leader;
- Culturally-sensitive to local area;
- Paternalism;
- Potential coercion;
- Genetics/homogeneity/validity to other populations;
- Language sensitivity;
- “Helicopter” Research (data/sample collection & leaving site with no follow-up);
- Infrastructure;
- Justify use of this population;
- Ethics body equivalent (Research Ethics Review Board/IRB/IEC) approval.

See the “International Compilation of Human Subject Research Protections” for information on research in specific countries such as Costa Rica, Venezuela, Uganda, and many more. And the International Guidelines Compiled by OHRP:

<http://www.hhs.gov/ohrp/international/HSPCompilation.pdf>

Some IRB members are familiar with specific international settings; when there is not an IRB member that knows of the culture being studied, a consultant in that culture may be utilized.

Further guidance on conducting international research is available for investigators on the OPHS website at:

<http://www.hsc.unt.edu/Sites/OPHSIRB/Documents/International%20Research%20by%20UNTHSC%20researchers.pdf>

Populations with No Written Language

When researchers work with populations who are not able to read or write, or those with no written language, obtaining informed consent can be challenging, and may not be feasible in some situations. The IRB will be concerned with the training of the researcher, and the process and procedures that will be in place to for an oral informed consent process. When appropriate, the investigator should use the English consent form as a template for translation into the oral language and include a statement about the process of informed consent. The consent form should be signed by the interpreter, the study Principal Investigator, and the subject, who will be requested to make a mark or thumb print, as appropriate. Investigators should contact OPHS staff for further guidance.

Minor Subjects (International research)

The IRB requirements for assent for minors in research studies are applicable. Written, parental permission is also required. If local customs and regulations are such that active parental permission would be culturally inappropriate, the researcher must supply the IRB with proof that such permission is not culturally appropriate. Examples of such proof would be specific regulations (in English and certified to be accurate) that indicate that such permission is not required, an official letter from a ranking official in the country of interest indicating that such permission is not culturally appropriate, or the appearance at an IRB meeting by someone of official standing in the research or academic community who can attest to the cultural inappropriateness of the requirement for active parental permission.

In those cases where seeking active parental permission for minors to participate in research is culturally inappropriate, a waiver of such permission may be granted at the discretion of the IRB, as long as the research does not place the subject(s) at untoward risk. Regardless of the type of risk, the subject(s) in the research retain(s) the right to discontinue participation, without penalty, at any time. If a waiver of active parental permission is granted, and if a letter informing the parents of the research is deemed appropriate, it must be written at a literacy level that would be understood by the parents, and should be sent to them by the most expeditious method possible.

Chapter 14: Student Research

CHAPTER CONTENTS

- Introduction to Student Research
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14.1 Introduction to Student Research

UNTHSC recognizes that some graduate student projects are conducted to fulfill course requirements, and that some projects are directed toward graduate degree activities that are research.

Current University policy states that students, pre-doctoral fellows, and medical residents cannot be the Principal Investigator on any research project involving human subjects. As such, a faculty member will need to be the Principal Investigator of record on such “student” projects.

For those student activities that are conducted solely to fulfill a course requirement, an element of the definition of research, the intent to develop or contribute to generalizable knowledge, is lacking. However, some of these classroom research assignments can place subjects at risk. Therefore, some classroom assignments may require OPHS and IRB review. Classroom assignments that involve research activities that are purely instructional and educational in nature, may not be subject to full IRB review according to the guidelines below. For more information, contact OPHS for assistance.

It is important to note that all student research presented at UNTHSC Research Appreciation Day (RAD) requires IRB review and approval. IRB approval should be obtained before submission of the online abstract. Students who do not obtain IRB approval before RAD will not be allowed to present their research at the event.

The Department of Health and Human Services (HHS) 45 CFR 46 defines a human subject as “a living individual about whom an investigator (whether professional or student) conducting research obtains..”

- Data through intervention or interaction with the individual, or
- Identifiable private information.

Intervention or Interaction

This 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

This includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place. Private information is information provided for specific purposes by an individual where the individual can reasonably expect such information 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.

Research

The Department of Health and Human Services (HHS) 45 CFR 46, defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

In accordance with federal regulations, the OPHS requires that all human subjects’ research be prospectively reviewed by an IRB. Accordingly, master’s theses, doctoral dissertations, postgraduate and medical resident research protocols involving human subjects must be submitted for OPHS review.

14.2 Student Course Assignments Involving Research with Human Subjects

Student course assignments involving research with human subjects may be defined by its purpose, or categorized into one of two areas:

- Category 1: to teach research techniques
- Category 2: research which leads to generalizable knowledge.

When in doubt, please contact the OPHS office for assistance.

While most classroom projects are not considered human subjects research, investigators are encouraged to follow the University's Code of Ethics and human research protection principles and procedures when designing and conducting projects with human volunteers.

Classroom research projects can be submitted to the OPHS, if desired by the professor of the course, for a human subjects research determination.

Projects in Category 1

Items such as the collection of information by students for the purpose of class discussion or for the purpose of training in research or research methods and program evaluation generally do not require OPHS review.

Projects in Category 2

The following class-related projects *do* require review by the IRB:

- All master's theses and doctoral dissertations that involve human subjects;
- All research projects involving human subjects that will be published or otherwise publicly disseminated, including posters (Research Appreciation Day (RAD), professional meetings, conferences etc.);
- Research projects involving human subjects through collaborations external to UNTHSC;
- Class-related projects for which identifiable data are collected and archived for any future research purposes other than administrative evaluations; and
- Classroom research that is more than minimal risk or involves vulnerable subject populations.

14.3 Requirements of Faculty Who Supervise Student/Fellow/Resident Research

Faculty should determine whether an assigned project involving human subjects is defined as a course- or training-related project. Faculty are strongly encouraged to contact the OPHS office for assistance in making this determination and for education on how to mentor students

through the IRB and human subjects research process. Faculty should discuss general principles of research ethics with the class prior to the initiation of any project involving human subjects. It may be possible to bundle similar studies conducted under one faculty advisor, decreasing the number of submissions that need to be submitted to the OPHS. Since federal regulations prohibit retroactive approval, no OPHS or IRB approval may be given **after** a classroom-assigned study is begun or completed.

Faculty Responsibilities for the Protection of Human Subjects

Faculty who supervise student/fellow /resident research are responsible for the protection of human subjects and are required to:

- Determine whether projects require IRB review and assist students with the process.
- Discuss research ethics with the students.
- Monitor student projects focusing on maintaining confidentiality, privacy, the level of risk, voluntary participation and withdrawal, and informed consent.
- Principal Investigators shall retain and maintain all records, including portable data storage devices such as flash drives, once the study is complete. Refer to section 7.6 for record retention requirements. Assure prompt reporting to the IRB of any event that requires reporting in accordance with the IRB principles and procedures for Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (refer to Section 17.5).

As Principal Investigator, the Faculty member associated with a student project is essentially responsible for everything that occurs regarding that project.

14.4 International Research Conducted by Students/Fellows/ Residents

For all international research (research occurring outside of the 50 U.S. states or territories), UNTHSC requires protocol review and approval by an outside IRB Ethical Review Committee (EC) or equivalent organization in the country where the research will occur in addition to UNTHSC IRB review, if applicable. If there is no local IRB, the principal investigator must obtain permission from the host entity to perform research in their facility. For example, if a UNTHSC student investigator is conducting research at an elementary school in China which does not have an affiliated IRB or EC, the student investigator must obtain written permission from the school in order to conduct their research. The elementary school in this example is, according to federal guidelines, “engaged in the research.”

Federal regulations acknowledge that local customs, norms, and laws where the research will take place may differ from the US regulations governing research, and they provide for accepting different standards in foreign assurances of compliance. At UNTHSC, policies for research studies conducted within the United States apply to international research wherever possible. In addition, international research protocols may include:

- Explanations of cultural differences that influenced the study design and the consent process;
- Rationale for conducting the study with an international population;
- Information regarding the host country's IRB, Ethical Review Committee or equivalent organization and documentation of its approval of the research, if applicable;
- A copy of the letter(s) of agreement on letterhead stationery with signatures from the local host institution(s), and from government officials, as necessary, to cooperate in the proposed research;
- A copy of the Informed Consent form, if used, in English, and a copy in the appropriate native language(s);
- Information regarding the literacy level of the expected subjects and how this may affect the informed consent process;
- A description of the informed consent process, including methods for minimizing the possibility of coercion or undue influence in seeking consent and safeguards to protect the rights and welfare of vulnerable subjects;
- A description of the processes for assuring anonymity and/or confidentiality of all data, and a description of the methods of transport and security of data to the United States, if applicable;
- If data will be collected by someone other than the researcher, the curriculum vitae of the individual and letters of agreement should be included on letterhead stationery and with original signatures from the research collaborators;
- If compensation is to be given to subjects, justification for the amount of money or goods should be provided and an explanation as to how this compensation is proportionate to the average annual income of people in the host country should be examined.

International studies will follow the same criteria for IRB review and approval as domestic studies. For example, a minimal risk study can receive an expedited review, whether the study is conducted within the US or abroad. See guidance available on the OPHS website for further

information at: <http://www.hsc.unt.edu/Sites/OPHS-IRB/Documents/International%20Research%20by%20UNTHSC%20researchers.pdf>

14.5 Students as Research Subjects

UNTHSC students are often participants in research studies on campus. In some cases, they may be the primary research participants, or enrollment in a study may be limited to students due to the topic of the research.

The major concern about students participating in research at UNTHSC is the vulnerability issue of coercion or undue influence. Students may feel as though they have to participate in research to please a professor, or may feel as if their grades, letters of recommendation, or other academic items may be connected with their decisions to participate in research. Consistent with an overall concern that no research subject should be coerced, researchers must take precautions to avoid the unintentional coercion or perception of a “requirement to participate” that can occur when potential research subjects are also students.

Researchers who wish to use their own students must be able to provide a good scientific reason, rather than convenience, for selecting their own students as research subjects. For example, the research project should be relevant to the topic of the class and participation should be part of the learning experience for the students.

In some circumstances, the IRB may require that someone other than the investigator (instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor, whether or not a student participated in the research project until after final grades have been determined. The students should be informed of these procedures in the Informed Consent form. In addition, it is generally recommended that the investigator/professor provide a recruitment flyer or letter to the students, so that the students may be the initiators and contact the investigator/professor regarding the research study.

14.6 Add-On or “Piggy-Back” Research Projects

“Piggy-Back” projects result when someone new (for example, a student or new faculty member) wants to engage in an IRB approved project and collect new data or generate a modification as a result of their specific interest/project that is not yet approved for that existing IRB-approved protocol.

One approach is for the current PI to modify the approved protocol and list the new person as key personnel. But since that double change would, in effect, be creating a separate sub-study, a better approach for this is to generate an entirely new protocol. This would more accurately reflect whatever newer interest, technique, blood draw, survey instrument, research question, add-on, and so forth was being created for a special project, and acknowledges that this “new” study will be accessing subjects / data streams coming from an existing IRB-approved project.

OPHS manages this *protocol double-change* (often known as a "pickaback" or "piggy-back" project) by requiring the "new" study PI to submit an application, protocol synopsis and all associated documentation for review. Further, that "new" sub-study packet will need a letter from the PI of the currently approved IRB project assuring and authorizing that the new sub-study PI does, in fact, have permission for and access to the subjects and/or the data. This keeps everything in compliance with federal regulations, allows such stand-alone projects to be reviewed without numerous modifications or delays to the existing study, and provides a better training experience for the new investigator, as well as increasing subject protection. See Chapter 6 for detail on submitting an application to the IRB.

Chapter 15: FDA Regulated Research

CHAPTER CONTENTS

- FDA Regulated Research: Introduction
- Investigational New Drug (IND) Exemption
- Investigational Medical Devices
- Emergency Use of an Investigational Drug, Biologic or Device
- Other FDA Policies and Considerations

Overview

This chapter covers research involving the use of the investigational drugs and biologics, investigational devices, emergency use of an investigational drug, biologic, or device, and other relevant FDA policies. Such use must adhere to Food and Drug Administration (FDA) regulations, as well as to Health and Human Services (HHS) regulations and state regulations.

FDA regulations have additional requirements for clinical investigations that involve the use of an approved product or biologic if it is used in a manner for which it is not approved. There are also additional FDA requirements for investigators conducting FDA regulated research. The FDA regulations for investigational drugs are outlined in 21 CFR 312, for investigations of medical devices in 21 CFR 812, and investigations of biological products in 21 CFR 600.

The current Good Clinical Practice (GCP) guidance of the FDA and of the International Conference on Harmonization (ICH), describe the responsibilities of the investigator with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations. Most (but not all) of these responsibilities and requirements are included in the investigator's signed statement, Form FDA-1572. Investigators and sponsors should refer to 21 CFR Parts 11. 50, 54, 56 and 312 for a more comprehensive listing of FDA's requirements for the conduct of drugs, biologics and device studies.

[See the following web links for FDA and ICH guidance:

FDA:

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationsheetsandNotices/default.htm>

ICH: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm> The IRB must give special considerations to two significant ethical issues: placebo-controlled trials and “washout” in drug treatment studies. Individual investigators must clearly define the nature and degree of risk to the subjects in the protocol and in the Informed Consent Form, and include risk management procedures and codification in the research plan.

Definitions for FDA Regulated Research:

- Biological product: A virus, therapeutic serum, toxin, antitoxin, vaccine, blood product, blood component or derivative, allergenic product, analogous product, or derivative applicable to the prevention, treatment, or cure of a disease or condition of human beings.
- Clinical investigation: Any experiment that involves a test article and one or more human subjects. Other commonly used terms include: research, clinical research, clinical trial, clinical study, study, and clinical investigation.
- Investigational new product: A new drug or biological product that is used in a clinical investigation.
- Device: "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
 1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
 2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
 3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

15.1 Investigational New Drug (IND) Exemption

Federal law prohibits the distribution of a new drug or biologic until the FDA reviews the clinical data and determines that the product is safe to use and is effective for a specified indication.

Investigators/sponsors who wish to test a new product must acquire an exemption before any testing

may begin. IND information must be included with any protocol submitted to the IRB that involves an investigational drug or biologic.

Investigators are required to submit to the IRB, the IND information provided by the sponsor, or, at a minimum, the current Investigator's Brochure and the Protocol; or, if the investigator is also the sponsor, a copy of the letter from the FDA that assigns the IND number will be required as part of the protocol application. The IRB will not release a final approval until the IND information is complete. OPHS and the Office of Clinical Trials (OCT) staff will be responsible for making sure this information is obtained prior to release of the approval notification and Informed Consent Form. If there is any question as to whether an IND is required, the IRB may require, as part of the review and approval process, that the investigator contact the FDA to discuss the protocol and to determine if an IND is required.

Investigators who propose to use investigational or marketed drugs for unapproved indications must also follow FDA regulations 21 CFR 50, 56 and 312. For the most part, the FDA regulations are the same as HHS regulations 45 CFR 46. Both sets of regulations are the same with regard to IRB organization, composition, procedure, record keeping, and criteria for approval of research protocol and Informed Consent Documentation. There are additional determinations that must be considered for protocols that involve the use of investigational products for unapproved indications.

For all investigations subject to IND regulations, the investigator is required to be knowledgeable about the requirements of FDA regulations and must be listed on the Statement of Investigator which is commonly referred to as the FDA Form 1572 <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf#search=%221572%22> in order to administer an investigational product. When it is determined that an IND is required, the research will not be approved until the IND information is submitted to the IRB. At the time of continuing review the IRB may request additional documentation (e.g., FDA Annual Report) to be certain the investigator is following the IND requirements.

Use of a Marketed Drug or Biologic in a Manner for Which It Is Not Approved: "Off Label Use"

When the FDA approves a drug or biologic it also includes the indications for which it is approved. Variance from the intended use is referred to as "off label use." Good medical practice and patient interest require that physicians use commercially available drugs and biologics in a knowledgeable way and with sound judgment. If a physician uses a product for an indication that is not in the approved labeling, they have the responsibility to be well-informed about the product and to base its use on firm scientific rationale and sound medical evidence. Use of a product for an individual patient in this manner may be considered "medical practice" and does not require submission of an IND or a protocol to the IRB. This may be considered "off label use."

"Investigational Use"

The investigational use of a marketed drug or biologic involves the use of an approved product in the context of a clinical study protocol. When the principal intent of the investigational use of a test product is to develop information about the product's safety or efficacy, submission of a protocol to the IRB is required. This is usually performed as a protocol with a hypothesis for a group of defined

patients. In this situation the intent is not solely to treat one patient but to look at a group of patients to answer a specific, predetermined set of questions. In addition, an IND will be required from the FDA. An IND will not be required if all the following conditions are met:

1. The study is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in labeling.
2. The study is not intended to support a significant change in the advertisement for the product.
3. The study does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product.
4. The study is conducted in compliance with the requirements for IRB review and informed consent.
5. The study is conducted in compliance with the requirements for the promotion and sale of drugs.
6. The study does not intend to invoke the requirements of 21 CFR 50.24 (exceptions from informed consent for emergency research).

When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires submission to the FDA for an IND, the investigator is advised to contact the FDA directly to determine if this is required. The IRB may require that an investigator contact the FDA if this has not been done at the time of IRB review. If the FDA indicates that an IND is not required, documentation of that stipulation from the FDA is required. This may be either a written notification from the FDA, or documentation of contact with the FDA, including who was contacted, the phone number, the time of the call, and a summary of the information provided by the FDA. This will allow for verification by OPHS and Office of Clinical Trials staff.

Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, test articles (investigational products) may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, a life-threatening, or a debilitating condition, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects, or the thoroughness and scientific integrity of product development and marketing approval.

Open Label Protocol or Open Protocol IND

These protocols are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued to enable the subjects and the controls to continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review of the protocol and informed consent.

Note that the protocol must be approved by the sponsor (if the protocol is itself not generated by the sponsor) and be accompanied by a letter from the sponsor giving permission to reference the sponsor's IND. Test article (drug, biologic, etc.) accountability must be addressed.

Treatment IND

A treatment protocol added to an existing IND is called a "treatment IND." The treatment IND 21 CFR 312.34 and 312.35 is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

1. The drug is intended to treat a serious or immediately life-threatening disease;
2. There is no satisfactory alternative treatment available;
3. The drug is already under investigation, or trials have been completed; and
4. The trial sponsor is actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent.

Parallel Track

The FDA's Parallel Track policy 57 FR 13250 permits wider access to promising new drugs for AIDS/HIV-related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establishing the safety and effectiveness of new drugs. It does so by providing an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

FDA Requirements for Investigators who are also Considered Sponsors of New Drugs:

Please review the federal regulations before performing any sponsor duties. If you are the sponsor and the investigator for the drug, you must meet the requirements for both the sponsor and the investigator.

Additional information may be found on the FDA's web site:
http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr312_00.html.

15.2 Investigational Medical Devices

Research with human subjects involving investigational medical devices must comply with FDA regulations for informed consent 21 CFR 50 and IRB 21 CFR 56 regulations. Investigational devices are medical devices undergoing clinical study to test the effectiveness and/or safety of the device and may be subject to the requirements of the Investigational Device Exemption (IDE) regulations 21 CFR 812. Investigational devices are classified as either non-significant risk devices (NSR) or significant risk devices (SRD).

The initial determination that a device is either a significant or non-significant risk device is made by the sponsor. If there is no external sponsor then the Principal Investigator (PI) is considered to be the sponsor. If the sponsor determines it to be a significant risk device, the proposed study must be submitted to the FDA. If the sponsor determines it to be a non-significant risk device, the proposed study is submitted to the IRB. The IRB makes an independent determination whether a device presents a non-significant or significant risk.

Definitions of Medical Devices

Medical device

In part, any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis of disease and other medical conditions such as pregnancy.

SR (Significant Risk) device

A device that presents a potential for serious risk to the health, safety, or welfare of a subject, and 1) Is intended as an implant; 2) Is used in supporting or sustaining human life; 3) Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or 4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

NSR (Non-Significant Risk) device

A device that does not meet the definition of a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the IRB regulations under 45 CFR 46.

510(k)

A new device determined by the FDA to be substantially equivalent to a device that was marketed prior to the passage of the Medical Device Amendments of 1976. Devices that qualify as 510(k) may be marketed immediately, without investigation of safety and efficacy. Research activities that involve a 510(k) do not require an IDE (see below) prior to approval by the IRB; however, the IRB will require written documentation that a 510(k) has been granted. This is usually obtained from the sponsor.

Investigational Device Exemption (IDE)

An exemption from certain regulations described in the medical device amendments that allows the shipment of an unapproved device for use in a clinical investigation. The sponsor of an SR device is required to apply to the FDA for an IDE before the clinical research may begin. There are abbreviated requirements for NSR devices that do not involve filing with the FDA.

Non-significant Risk Devices

The sponsor is responsible for the initial determination that a device presents non-significant or significant risk. The proposed study is then submitted to IRB for review. The IRB submission should include the following information: the sponsor's risk assessment determination; the rationale for the non-significant risk determination (why the sponsor believes the device presents no significant risk to study subjects with supporting information including reports of prior investigations); whether other IRBs have reviewed the proposed study and if so what determination was made; and, if the device has been reviewed by FDA, the FDA's assessment of the device's risk. The IRB may also consult the FDA for its opinion.

The IRB will make an independent determination of device risk. Examples of non-significant risk devices are: low power lasers for treatment of pain; caries removal solution; daily wear contact lenses; conventional gastroenterology and urology endoscopes; conventional laparoscopes, culdoscopes, and hysteroscopes. Additional examples may be obtained from the UNTHSC Clinical Trials Office. In deciding if a device presents significant or non-significant risks, the IRB must consider the device's total risks, not as compared with the risks of alternative devices or procedures. The risk determination must consider the proposed use of the device in the investigation not on the device alone. If the device is used in conjunction with a procedure involving risk, the IRB must consider the risks of the procedure in conjunction with the risks of the device.

If the IRB determines the device is a non-significant risk device, an IDE application submission is not required. The IRB will then review the proposed research study as indicated in this document. If the study is approved by the IRB the study must be conducted in accordance with the "abbreviated requirements" of the IDE regulations 21 CFR 812.2(b).

If the device is exempt from the IDE regulations, the investigator must categorize the device as belonging to one or more of the categories:

This is a legally marketed device when used in accordance with its labeling.

- This is considered a diagnostic device if it complies with the labeling requirements in §809.10(c) and, if the testing is noninvasive, does not require an invasive sampling procedure that presents significant risk; does not by design or intention introduce energy into a subject; and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.
- The device is used under consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved, cleared Pre-market Notification (PMA) 510(k), or are exempt from 510(k) requirements] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

If the device qualifies for an abbreviated IDE [non-significant risk devices (NSR)], the investigator must include a statement from the sponsor or sponsor/investigator indicating that the device poses a non-significant risk of harm to the study subjects **OR** documentation from the sponsor with an explanation of its NSR determination and any other information that may assist the IRB in evaluating the risk of the study including:

- The sponsor should provide the IRB with a description of the device;
- Reports of prior investigations with the device;
- The proposed investigational plan;
- A description of patient selection criteria and monitoring procedures;
- As well as any other information that the IRB deems necessary to make its decision.
- The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made.
- The sponsor must inform the IRB of the FDA's assessment of the device's risk if such an assessment has been made.

The investigator must submit this information with the IRB application. If the IRB determines the device is a significant risk device, the IRB will notify the investigator and the sponsor of this determination. The sponsor must notify FDA when the IRB determines that a device, judged by the sponsor not to present a significant risk, should be categorized as a significant risk device.

Significant Risk Devices:

The sponsor is responsible for the initial determination that a device presents non-significant or significant risk. A significant risk device by definition is an investigational medical device that may present a serious risk to the health or safety of the research subjects. Such a device is:

- Intended for use as an implant; or
- Purported to be useful in supporting or sustaining human life; or
- Intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
- One that otherwise presents a serious risk to the health, safety, or welfare of subjects.

The IRB must make an independent determination of device risk. Examples of significant risk devices are pacemakers, IUDs, some laser systems, and some hemodialysis systems. Additional examples may be obtained from the UNTHSC Clinical Trails Office. In deciding if a study poses a significant risk, the IRB will consider the nature of the harm that may result from use of the device in an investigation, and not on the device alone. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered significant risk. If the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

If the IRB determines the device to be significant risk, then an IDE application to the FDA and FDA approval of the investigation must be obtained before the IRB reviews the study. The investigator must specify the IDE number in the IRB application and attach a copy of the FDA letter indicating approval when available. After an IDE is obtained by the sponsor, the IRB will then review the proposed research study as indicated in this document. As with non-significant risk devices, IRB approval is required and maintained throughout the investigation. Informed consent must be obtained and documented. The study must be conducted according to IDE regulations 21 CFR 812. Studies of significant risk devices present more than minimal risk; thus, full board IRB review for all studies involving significant risk devices is necessary.

New (Including IDE) Devices

Summary of FDA Requirements for Investigators who are Also Considered Sponsors of New Devices:

The following is an overview of the FDA requirements for sponsors with an IDE. This overview is divided into two sections: Responsibilities of Sponsors for Significant Risk Device Studies and Responsibilities of Sponsors for Nonsignificant Risk Device Studies. It cites the appropriate FDA regulation for each item. Before referencing the overview, please review the federal regulations 21 CFR 812.3(m) to determine if the device is a Significant Risk Device or a Nonsignificant Risk Device. If an investigator is also the sponsor for a device, the following requirements must be met.

Major Responsibilities of Sponsors for Significant Risk Device Studies

- Obtain FDA and IRB approval for IDE. (21 CFR 812.42)
- Select investigator(s) with appropriate training and experience. (21 CFR 812.43)
- Select monitor in accordance with FDA regulations. (21 CFR 812.43)
- Ship investigational devices only to qualified investigators. (21 CFR 812.43)
- Obtain a signed agreement from the investigator using the required FDA documents. (21 CFR 812.43)
- Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations. (21 CFR 812.45)
- Ensure that investigator(s) are complying with FDA, IRB, and sponsor requirements. (21 CFR 812.46)
- Conduct an evaluation of unanticipated adverse events and terminate the study if necessary.(21 CFR 812.46)
- Resume terminated studies only after receiving approval from the FDA and IRB (21CFR 812.46)
- Maintain accurate and complete records in accordance with FDA regulations.(21 CFR 812.140)
- Provide required reports to IRB, investigator(s), and FDA in a timely manner.(21 CFR 812.150)
- Label the device in accordance with FDA requirements. (21 CFR 812.5)
- Promote the device in accordance with IRB and FDA requirements.(21 CFR 812.7)
- Comply with federal regulations regarding emergency use. (21 CFR 812.47)

Major Responsibilities of Sponsors with Non-significant Risk Device Studies

- Label the device in accordance with FDA requirements. (21 CFR 812.5)
- Obtain IRB approval of the investigation as a non-significant risk device study and maintain IRB approval during the investigation. (21 CFR 812.2)

- Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver. (21 CFR 812.2)
- Comply with FDA requirements for monitoring the study. See items 7-9, above, for monitoring requirements. (21 CFR 812.46)
- Maintain accurate and complete records in accordance with FDA regulations, and report the results to the FDA, IRB, and investigators. (21 CFR 812.140 and 21 CFR 812.150)
- Ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties. (21 CFR 812.140 and 21 CFR 812.150)
- Promote the device in accordance with IRB and FDA requirements. (21 CFR 812.7)

15.3 Emergency Use of an Investigational Drug, Biologic or Device

From the FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update.

Emergency Use of an Unapproved Investigational Drug or Biologic

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is for the Investigator to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

Emergency use is defined as the use of an investigational drug or biological product in a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval 21 CFR 56.102(d). The emergency use provision in the FDA regulations 21 CFR 56.104(c) provides exemption from prior review and approval by the IRB. The exemption, which may not be used unless the subject is in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available, allows for **one** emergency use of a test article without prospective IRB review.

Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a

life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the IRB expects the investigator to complete an IRB application describing the emergency use. The proposal will be scheduled for review at the next IRB meeting. The FDA regulations require that any subsequent use of the investigational product at the institution has prospective IRB review and approval. Therefore, if the first use does not have prospective review, the IRB notifies the investigator that if it is possible that subsequent use of the agent will occur; an IRB application should be submitted for IRB review immediately following the first emergency use. The FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The investigator must notify the IRB Chair prior to the emergency use. However, this notification should not be construed as IRB approval. The investigator is required to file a written report within five working days, and notifying the Chair is used to initiate tracking to ensure that the investigator files this report as required by 21 CFR 56.104(c).

The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must either convene or give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB Chair will send the investigator a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an "IRB approval," in the past, an acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

Emergency Use of Unapproved Investigational Drug or Biologic Without IRB Approval

Use may proceed without any prospective IRB approval when all of the following conditions exist:

1. The use of the test article (investigational drug, or biological) in a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.
2. The exemption allows for one emergency use of a test article without prospective IRB review.
3. The UNTHSC IRB must be notified prior to such use. Notification may be by telephone, voice mail, or FAX (323-224-8389). This notification is used by the IRB to

initiate tracking to ensure that the investigator files a report within the five-day time frame.

4. The IRB must receive written notification within five working days of the emergency use. Notifications will be reviewed at the next convened IRB meeting. Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: The subject is confronted by a life-threatening situation necessitating the use of the test article; Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject; Time is not sufficient to obtain consent from the subject's legal representative; and No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
5. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB promptly, not to exceed five working days after the use of the test article.

Any subsequent use of the investigational product requires prospective IRB review and approval. Subsequent use includes a second use with the first subject or the use with another subject. Therefore, if it is anticipated that the test article may again be used, the IRB will require the complete IRB application, Informed Consent Form, clinical protocol, investigators brochure, and any supporting information deemed necessary for review, be developed and submitted so that an approved protocol would be in place when the next need arises. These documents must be submitted for full board review.

Emergency use of a test article in a life-threatening situation represents an exemption from IRB review. According to FDA regulations, the exemption does not apply if the IRB has the time to prospectively review such uses and the FDA regulations make no provisions for retrospective approval of research.

Emergency Use of an Unapproved Device:

The IRB allows for the emergency use of an unapproved device if the FDA requirements for emergency use are met and the IRB office is notified (whenever possible) of an intent to use an unapproved device.

Emergency use of an unapproved device is defined as the use of an unapproved device for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval (FDA approval for marketing) with a human subject in a life-threatening situation where the unapproved device may offer the only possible life-saving alternative, but an IDE for the device does

not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE.

Using its enforcement discretion, the FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to the FDA that an emergency actually existed.

Emergency Use of an Unapproved Device without IRB Approval

Use may proceed without prospective IRB approval as follows:

1. All of the following conditions must exist: the patient is in a life-threatening condition that needs immediate treatment; no generally acceptable alternative for treating the patient is available; and because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.
2. The physician should obtain an independent assessment by an uninvolved physician.
3. The IRB should be notified prior to such use. Notification may be by telephone, voice mail or FAX.

This notification is used by the IRB to initiate tracking to ensure that the investigator files a report within the five-day time frame. OPHS staff review the proposed use and determine whether: (1) The circumstances of the proposed use meet the requirements for exemption from the requirement for IRB review under 21 CFR 56.104(c) and; (2) Informed consent will be obtained and documented in accordance with 21 CFR 50.20, 50.25 and 50.27 or whether the circumstances meet the exception from the requirement to obtain informed consent in 21 CFR 50.23. IRB staff will inform the investigator whether the use meets regulatory requirements and provide assistance on compliance. If the use does not meet regulatory requirements, IRB staff notifies the investigator that proceeding with the emergency use as described will violate federal regulations.

The IRB must receive written notification within five working days of the emergency use. Notifications will be reviewed at the next convened IRB meeting.

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: The subject is confronted by a life-threatening situation necessitating the use of the test article; Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; Time is not sufficient to obtain consent from the subject's legal representative; and No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical

investigation. The investigator must notify the IRB promptly, not to exceed five working days after the use of the test article.

If an IDE exists, authorization from the IDE holder should be obtained. If an IDE for the use does not exist, the sponsor is to be notified of the emergency use. If an IDE does not exist the FDA must be notified of the emergency use (Center for Devices and Radiological Health—CDRH Program Operation Staff 301-594- 1190) and provided with a written summary of the conditions constituting the emergency, subject protection measures and results.

Any subsequent emergency use of the investigational device requires an IDE and prospective IRB review and approval. If it is anticipated that the investigational device may be used on subsequent subjects, the IRB will require the IRB application, Informed Consent Form, clinical protocol, investigators brochure, and any supporting information deemed necessary for review, be developed and submitted so that an approved protocol would be in place when the next need arises. These documents must be submitted for full board review.

Informed Consent Requirements in Emergency Research

When the need for a waiver of informed consent is necessary for emergency research, the UNTHSC IRB follows the regulations as stipulated by both the FDA and DHHS. The FDA published in the Federal Register in September 1995 a proposal to amend its regulations to permit a limited class of research in emergency settings without consent. A final regulation was published in the Federal Register on October 2, 1996. HHS also published its waiver criteria which match the FDA requirements.

Exception from Informed Consent Requirements for Emergency Research

The IRB may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

- The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

Obtaining informed consent is not feasible because:

- The subjects will not be able to give their informed consent as a result of their medical condition;
- The intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and

- There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the research.

Participation in the research holds out the prospect of direct benefit to the subjects because:

- Subjects are facing a life-threatening situation that necessitates intervention;
- Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
- Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- The research could not practicably be carried out without the waiver.
- The proposed research protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact representatives and make this information available to the IRB at the time of continuing review.

The IRB has reviewed and approved informed consent procedures and an Informed Consent Form in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. These procedures and the Informed Consent Form are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph (b)(7)(v) of this waiver.

Additional protections of the rights and welfare of the subjects will be provided including, at least:

- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
- Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the research, of plans for the research and its risks and expected benefits;

- Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
- Establishment of an independent data monitoring committee to exercise oversight of the research; and
- If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether they object to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the Informed Consent Form. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that they may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least three years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with § 56.115(b) of this chapter.

Protocols involving an exception to the informed consent requirement under this section must be performed under a separate IND or IDE that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §§ 312.30 or 812.35.

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the

clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

15.4 Other FDA Policies and Considerations

Personal Importation and Use of Unapproved Products

The FDA permits individuals to bring into the United States, for their own personal use, up to a three month supply of FDA-regulated products sold abroad but not approved in the United States. Importation may be in personal baggage or by mail. All of the four following conditions must be met in order to permit importation:

1. The product was purchased for personal use.
2. The product is not for commercial distribution and the amount of product is not excessive (i.e., three-month supply or less).
3. The intended use of the product is appropriately identified.
4. The patient seeking to import the product affirms in writing that it is for the patient's own use and provides the name and address of the licensed physician in the U.S. responsible for his or her treatment with the product.

This FDA importation policy applies to most drugs, biologics and medical devices intended for personal import, provided they are not fraudulently promoted and do not present an unreasonable risk. Importation by a physician for use by their patients does not meet the requirements for personal importation. Since the person using the product initiates the importation, that person is presumed to be knowledgeable about the product and its use. Therefore, such personal importation is not regarded by the FDA to be research and an IND/IDE is not required. Also, neither IRB review nor informed consent is required by FDA for such personal importation and use.

The IRB will acknowledge in writing the request made by an investigator for a subject's personal importation and use of an unapproved product and note that all four of the above conditions have been met. This action will be forwarded to the next convened IRB meeting for information only.

Humanitarian Use Devices 21 CFR 814:

The FDA finalized regulations regarding humanitarian use devices (HUD) in 1996. The purpose of this classification is to foster the development of devices to diagnose or treat conditions that do not occur frequently. The reasoning behind these regulations is that these types of devices may not be developed if extensive clinical testing was required because of the limited market potential.

Definitions

Humanitarian Use Device (HUD): As defined in 21 CFR 814.3, a humanitarian use device (HUD) is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

Humanitarian Use Device Exemption (HDE): An HDE is an application similar to a FDA premarket approval application. However, an HDE application is not required to present evidence of effectiveness to the degree that is usually required for FDA approval.

UNTHSC IRB Review of HUD

It is important to understand the unique role of the IRB related to HUDs. FDA regulations require that the IRB approve the use of a HUD to treat or diagnose a medical condition as specified in the HUD. This is the only situation in which federal regulations require IRB review and approval of an activity that is clearly not research.

Initial IRB review and continuing review (at least annually) will be required for all HUD at UNTHSC.

When requesting IRB review of a HUD, a letter or document from the device sponsor should be submitted to OPHS that includes the following information:

1. The generic and trade name of the device
2. The FDA HDE number
3. The date of the HUD registration
4. Indications for use of the device
5. A description of the device
6. Contradictions, warnings, and precautions for use of the device
7. Adverse effects of the device on health
8. Alternative practices and procedures
9. Marketing history
10. Summary of studies using the device.

Additionally, the PI must provide documentation to the IRB that the HUD is not being used as part of a research project or clinical investigation designed to collect data to support an FDA premarket approval application. If the HUD is being used as a part of a research or clinical investigation, the IRB must comply with all of the FDA regulations related to IRB review of research.

The IRB has the authority to determine the conditions of the HUD use, and may limit the use of the HUD based upon any criteria that it deems appropriate.

There is no time limit on the FDA approval of an HDE. HDE applications do not have to be renewed. Additionally, there is no regular required correspondence between the FDA and the HDE applicant after the application has been approved. After initial review and approval, continuing review of the HUD by the IRB will be required at least annually.

Federal regulations do not require informed consent to use an HUD outside of a research setting. However, the IRB may require the investigator to develop an Informed Consent Form specific for the use of the HUD. If so, all references to research must be eliminated from the Informed Consent Document.

Investigators or sponsors will not be required to submit the names and addresses of the IRB(s) that approved the use of the HUD to the FDA.. However, they will be required to maintain appropriate records of all correspondence with the reviewing IRB (s).

Further FDA guidance related to HUDs and HEDs is available at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071473.htm>

Please contact OPHS staff for additional guidance on this topic.

Dietary Supplements

The FDA has finalized rules that define the types of statements that may be made concerning the effects of dietary supplements on the structure or function of the human body. The increased use of supplements has led to an increase in research. The FDA requires research that involves dietary supplements, that is undertaken for the purpose of investigating the effects of prevention, cure, mitigation, or diagnosis of disease, to abide by IND requirements before testing may begin. The investigator is to check with the FDA when developing a protocol that involves the use of dietary supplements. The IRB may also require that the FDA be contacted if the investigator has not already done so.

15.5 Registering a Clinical Trials (Clinical Trials.gov)

Background

Public Law 110-85, enacted in September 27, 2007 requires that “applicable trials” be registered on the NIH’s website, “ClinicalTrials.gov”. Under the statute, these trials generally include:

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;

- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.

For clinical trials, the sponsor of the trial (as defined in 21CFR 50.3) is responsible for complying with the requirement to register the trial. The Principal Investigator (PI) or, if delegated, the Study Coordinator is responsible for corresponding with the sponsor to ensure that the sponsor includes the UNTHSC-FW site location under the Contacts and Locations section of the study-specific tab on “[ClinicalTrials.gov](https://clinicaltrials.gov)”. If the sponsor declines to include the UNTHSC-FW site, the PI or designee will notify the Office of Clinical Trials.

For Investigator-Initiated clinical trials that do not involve FDA regulated drugs, biologics or devices as described above, the trial is not required by law to be listed on ClinicalTrials.gov; however, the investigator nonetheless may wish to register the trial and should do so through the Office for the Protection of Human Subjects (OPHS) at UNTHSC (but only after first having obtained UNTHSC IRB approval for that trial).

Here is a link to US Public Law 110-85: <http://prsinfo.clinicaltrials.gov/fdaaa.html>

Principal Investigator Responsibilities

From a UNTHSC investigator’s point of view, in almost all cases, a research investigation involving a drug, device or biologic requiring registration at ClinicalTrials.gov will have been registered by the sponsor and no further registration action is required by the UNTHSC researcher.

Since all industry sponsored drug, biologic or device studies at UNTHSC must first be processed through the Office of Clinical Trials, and, since the sponsor is the responsible party for registration, a clinical trial principal investigator at UNTHSC would not register that trial.

Thus, individual clinical investigators at UNTHSC do NOT need to register their project(s) at ClinicalTrials.gov.

Registering “clinical trials” that do not meet the requirements of the federal law

Occasionally, some journals and some funding agencies may require that an investigator provide evidence that their research project is listed on a “public registry”, even if that study does not involve a drug, device or biologic subject to FDA regulation.

For example, some research involving physical therapy, osteopathic manipulations or psychological interventions may be considered “clinical research” by journal editors or funding agencies, and thus require that such projects be listed on a public registry.

Note that these special situations for registration are not a requirement of federal law, but a stipulation of that particular journal or funding source. In such cases, the project may be listed at ClinicalTrials.gov but only through submission to OPHS. Since the registration process is somewhat cumbersome and information-intensive, OPHS will assist with this registration service to UNTHSC

researchers seeking a public registration of their project, on a case-by-case basis. [Again, recall that only FDA regulated research is legally required to be registered at [ClinicalTrials.gov](https://clinicaltrials.gov)].

To minimize unnecessary paperwork and resource allocations, OPHS requires written documentation from the journal or funding agency that specifically states that the project needs to be registered at [ClinicalTrials.gov](https://clinicaltrials.gov) or some other public research registry.

To inquire about the need to register your clinically-oriented research project, and for any questions about the [ClinicalTrials.gov](https://clinicaltrials.gov) registration process, contact OPHS for details.

Chapter 16: Health Insurance Portability and Accountability Act (HIPAA)

Overview

This chapter describes the “Privacy Rule,” also known as HIPAA (Health Insurance Portability and Accountability Act), designed to establish minimum federal standards for safeguarding the privacy of an individual’s identifiable health information. Additionally, the role and requirements of the UNTHSC IRB, as related to HIPAA and HIPAA authorization information, can be found in this chapter.

16.1 Health Insurance Portability and Accountability Act (HIPAA)

HIPAA’s Privacy Rule went into effect April 14, 2003 <http://www.hhs.gov/ocr/hipaa>. The law generally prohibits health care providers such as health care practitioners, hospitals, nursing facilities and clinics from using or disclosing protected health information without written authorization from the individual (HIPAA Authorization).

Protected Health Information (PHI)

Any identifiable health information relating to the individual's past, present or future physical or mental health condition or payment for health care is considered protected health information. When health information is individually identifiable and is held by a “covered entity” (under the Privacy Rule a covered entity is defined as: a health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which HHS has adopted a standard), it is likely to be protected health information. The HIPAA rule governs the use of individually-identifiable health information when it is protected health information (PHI). HIPAA defined categories of PHI:

1. Patient names;
2. Dates (except year) directly related to an individual (e.g., DOB, death, hospital admission, and discharge);
3. Patient postal addresses including city, state, & zip code;

4. Patient telephone numbers;
5. Patient fax numbers;
6. Patient e-mail addresses;
7. Patient social security numbers;
8. Patient medical record numbers;
9. Patient health plan ID numbers;
10. Account numbers;
11. Certificate/license numbers belonging to a patient;
12. Patient vehicle identifiers;
13. Device identifiers and/or device serial numbers specific to a particular patient;
14. URLs;
15. IP address numbers;
16. Biometric identifiers, including finger and voice prints, belonging to a patient;
17. Full face photos and other comparable images of a patient;
18. Any other unique patient-identifying characteristic or code.

HIPAA allows a covered entity to use or disclose de-identified personal health information without restriction. Under this method, the above 18 elements that can identify the individual or the individual's relatives, employers, or household members must be removed from the health information. De-identifying PHI enables many research activities to go forward; however, researchers often need access to protected health information to gain meaningful results from the health information. Where PHI is needed for research activities, the Privacy Rule permits its use and disclosure if certain standards are met, (see link) and the individual signs a HIPAA authorization form (can be waived by the IRB in some cases).

HIPAA Limited Data Set / Data Use Agreement

The rules governing use of a limited data set provide options to the researcher. Limited data sets are not fully de-identified. A limited data set must not include direct or facial identifiers like name, social security number, full-face photos or medical record number.

A limited data set may include, however, zip codes, dates of service, dates of birth and death and geographic information (not street address). A covered entity may use and disclose a limited data set for research activities conducted by itself, another covered entity or a

researcher who is not a covered entity, if the disclosing covered entity and the limited data set recipient enter into a data use agreement. This data use agreement is the means by which covered entities obtain satisfactory assurances that the recipient of the limited data set will only use or disclose the PHI in the data set for specified purposes.

Waiver or Alteration of Individual HIPAA Authorization

Other research activities can be performed without an individual's HIPAA authorization, a waiver or alteration of HIPAA authorization, or a data use agreement. For example, this could include activities involved in preparing for research and in using or disclosing the PHI of the deceased for research. Under the preparatory to research provision, a covered entity may permit a researcher to use PHI for purposes preparatory to research. However, the covered entity must obtain from a researcher, representations that 1) the use or disclosure is requested solely to review the PHI as necessary to prepare a research protocol or for similar purposes preparatory to research; 2) the PHI will not be removed from the covered entity in the course of review; and 3) the PHI for which use or access is requested is necessary for the research.

The Privacy Rule imposes a minimum necessary requirement on all permitted uses and disclosures of PHI by a covered entity. This means that a covered entity must apply policies and procedures, or criteria it has developed, to limit certain uses or disclosures of PHI.

[The Privacy Rule is in Title 45 of the Code of Federal Regulations, in Part 160 and in Subparts A and E of Part 164. The full text of the Privacy Rule can be found at the HIPAA Privacy Web site of the Office for Civil Rights (OCR): <http://www.hhs.gov/ocr/hipaa>.

Role of the UNTHSC OPHS and IRB Related to HIPAA

The UNTHSC OPHS and IRB are charged with ensuring that all researchers and investigators accessing protected health information are HIPAA compliant. (This HIPAA role is an assigned task in addition to the IRB procedures. In some institutions a privacy board fills the HIPAA role.)

In this capacity, the IRB will determine whether: 1) the research subject must sign a UNTHSC HIPAA Authorization Form, in addition to the Informed Consent Form from the covered entity, to obtain their authorization for research use or disclosure of PHI; or 2) a Waiver of HIPAA Authorization, either for being a research subject and/or for screening/recruiting subjects, will be granted. In addition, it is a UNTHSC policy requirement that *all* employees and students complete UNTHSC's HIPAA on-line educational program <https://www.hsc.unt.edu/HIPAATrain/>

For more detailed information regarding HIPAA policies, forms, and procedures, please go to the Office of Compliance's website: <http://www.hsc.unt.edu/departments/InstitutionalCompliance/>

NOTE: Even if some research projects involving human subjects may meet the EXEMPT (from IRB review) research category, they may still require HIPAA authorization or waiver.

Please check with OPHS for guidance anytime you re conducting research that involves medical and/or health information of any person.

Chapter 17: Noncompliance, Unanticipated Problems, Administrative Hold, Suspension, Closure or Termination of Approved Research, Reporting Protocol Violations

CHAPTER CONTENTS

- **Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others, and Serious and Unexpected Adverse Events**
- **The Process for Handling Reports of Alleged Noncompliance**
- **Administrative Hold, Closure, Suspension / Termination of IRB Approved Human Subjects Research**
- **Reporting Requirements (Unanticipated Problems Involving Risk to Subjects or Others, Serious or Continuing Noncompliance, and Suspensions / Terminations**
- **Reporting Protocol Violations**

Overview

This chapter outlines the procedures taken when issues of noncompliance, unanticipated problems involving risks to subjects or others, and adverse events in human subjects research come to the attention of the IRB. It describes the responsibilities of the OPHS staff, Principal Investigator, IRB committee, and IRB Chair, and the steps required to rectify the situation.

17.1 Procedure for Handling Reports of Unanticipated Problems Involving Risk to Subjects or Others and Serious and Unexpected Adverse Events

OPHS Staff Responsibilities

Upon receipt of a report of an unanticipated problem involving risk to subjects or others, or a serious and unexpected adverse event, the OPHS staff promptly forwards the report to the Director, OPHS and then to the IRB Chair or designee. Reports **without a change** to the potential risk/benefit ratio, study protocol or Informed Consent Documents are reviewed and acknowledged by the IRB Chair.

Reports that **include a change** in the potential risk/ benefit profile, study protocol or Informed Consent Documents, are prepared for full IRB review. For consideration, the event must be serious, unanticipated, and related to the study. If subjects are at immediate risk of harm and there is insufficient time to wait for review by the convened IRB, the Chair/designee may immediately halt further enrollment.

In any case, the OPHS staff assigns the item(s) to the next full board agenda. All board members will then have access to:

- The report of unanticipated problem involving risk to subjects or others or serious and unexpected adverse event;
- The Data Safety Monitoring Board (DSMB) or safety report, if applicable;
- Any attached supplemental material submitted with the report;
- An amendment request, if applicable;
- The current IRB approved application, which includes (if applicable) the Informed Consent Documents, sponsor's protocol, investigator's brochure, and
- Any other pertinent materials such as advertisements, questionnaires, etc.
- Unanticipated problems involving risk to subjects or others are acknowledged through expedited review procedures and are included on the next available agenda for board notification.

IRB Committee Responsibilities

If the IRB determines that the event meets all three criteria (serious, unanticipated, and related), the event is considered an unanticipated problem involving risks to subjects or others. The IRB considers any number of the following actions:

- Accept the report with no changes;
- Accept the report with changes to the potential risk/benefit ratio, the protocol, or the Informed Consent Documents;
- Require re-consenting of subjects or require notification to subjects (including past subjects) of the changes. The changes must be reviewed by the IRB prior to notification;
- Request further information from the investigator or the DSMB;
- Increase the frequency of continuing review;
- Impose additional monitoring by the Office for Protection of Human Subjects (OPHS), or an independent monitor;
- Halt enrollment pending receipt of further information;
- Report findings as appropriate depending on the nature of the event;
- Suspend any of the following activities:

-Screening and enrollment;

-Recruitment;

-Intervention and interaction; or

-Follow up;

-Terminate IRB approval of the study according to IRB policy.

In the case of deviations from the protocol initiated by the Principal Investigator (PI) without prior IRB review to eliminate apparent and/or immediate hazard to a research subject, the IRB will consider whether the changes were consistent with the rights and welfare of subjects.

17.2 The Process for Handling Reports of Alleged Non-Compliance

The UNTHSC IRB upholds its role in assuring prompt reporting of any serious or continuing noncompliance with 45 CFR Part 46, 21 CFR Part 56, or the requirements or determinations of the IRB.

Definitions

Noncompliance: Failure to follow the regulations governing human research or failure to follow the requirements or determinations of the IRB. This definition includes action of any University employee or agent, such as investigators, research staff, IRB member, OPHS staff, employees or institutional officials.

Serious Noncompliance: An action or omission taken by an individual (e.g., investigator, research staff, IRB member, OPHS staff, employee or institutional official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject.

Continuing Noncompliance: A pattern of repeated actions or omissions taken by an individual (e.g., investigator, research staff, IRB member, OPHS staff, employee or institutional official) that indicates a deficiency in the ability or willingness of an individual to comply with federal regulations, UNTHSC IRB policy, or determinations or requirements of the UNTHSC IRB.

All reports of alleged noncompliance or inappropriate involvement of humans in research are investigated by OPHS, the IRB, or both when appropriate. Such reports may come from any source such as an IRB member, an investigator, a subject or their family members, institutional personnel, other institutional committees, the media, anonymous sources, or the public. Goals of the IRB, in general, in investigating and managing issues of potential noncompliance include:

- Assuring the safety of human participants;
- Developing “Corrective and Preventative Action” (CAPA) plans to prevent reoccurrence, and promote future compliance;
- Educating research staff to assure the understanding of the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) guidelines and regulations, and UNTHSC human research protection (OPHS and IRB) principles and procedures;
- Reporting serious or continuing noncompliance.

Handling Allegations of Noncompliance:

OPHS Staff Responsibilities

The OPHS Staff receives a report of alleged noncompliance, reviews it and contacts the investigator if more information is needed. The report is then given to the Director, OPHS and the IRB Chair for determination. If both the Director, OPHS and the IRB Chair determine the allegation to be without substantiation, the matter is filed within the appropriate protocol document folder.

Otherwise, the matter is handled as a finding of noncompliance. If the Director (OPHS) or the IRB Chair is unable to make a determination, the OPHS staff facilitates review of the report by the full IRB. All communications between the investigator and the IRB are retained. The OPHS staff notifies the PI in writing of IRB determinations. The letter requires a signature of the IRB Chair or his/her designee.

Handling Findings of Noncompliance:

OPHS Staff Responsibilities

When the OPHS staff receives a report of a finding of noncompliance, he/she verifies whether a detailed explanation accompanies the report and gives it to the IRB Chair. The Chair determines if the information is serious and meets the definition of noncompliance, or if more information is required to make a determination. If the information does not meet the definition of noncompliance, the IRB Chair:

1. Formulates a Corrective and Preventative Action plan;
2. Forwards the Corrective and Preventative Action plan to the investigator; and
3. Forwards the report of a finding of noncompliance to the convened IRB for review.

If the IRB Chair determines the information is serious or inhibits the rights or welfare of participants, the information is forwarded to the full IRB for review. The OPHS staff prepares the following documents for full board review:

1. Audit report (investigation report);
2. Notification of noncompliance, if applicable;
3. Pertinent IRB correspondence (e.g. IRB applications, IRB approval letters, IRB approved informed consent, etc.)
4. At least one IRB member will be provided with and required to review the protocol for the study in question.

If more information is needed, the Chair directs an investigation by the OPHS compliance auditor or designee. The investigator is notified in writing of the directed investigation (audit). [See Chapter 20 for more information regarding audit procedures.] The audit report is presented to the IRB chair and reviewed at the next full board meeting. It is possible that an investigation by the OPHS can occur simultaneously with review by other UNTHSC offices (e.g., Compliance Office, Conflict of Interest Committee, Office of Research, University Counsel, etc.).

IRB Committee Responsibilities

The IRB committee reviews the materials provided at a convened meeting to determine:

1. There is no compliance issue(s) related to IRB policies, guidelines, or procedures;
2. There is noncompliance. The OPHS office will report this determination according to UNTHSC policy;
3. There is insufficient information to make a determination. In this case, the IRB will request additional information from the OPHS, Investigator or other UNTHSC offices (e.g., Compliance Office, etc.) and defer a determination to a later convened IRB meeting.

The IRB Committee may determine the following added protections, if applicable:

- Verification that subject selection is appropriate and observation of the actual informed consent process as determined by OPHS staff;
- An increase in monitoring of the research activity via a data safety monitoring board and / or continuing evaluation of the site by OPHS staff;
- Request a directed audit of targeted area(s) of concern;
- Request a status report after each subject receives intervention from the investigator;
- Modify the continuing review cycle;
- Request additional investigator and staff education focused on human research protections from the OPHS staff or other available sources (e.g., Institutional Biosafety Committee (IBC), Radiation Safety Committee (RSC), OHRP conferences, National Institutes of Health (NIH) tutorial, human research protections seminars, etc.);
- Notify current subjects, if the information about the noncompliance might affect their willingness to continue participation;
- Suspend or terminate the study;
- Require modification of the protocol;
- Require information to be disclosed during consenting, and/or re-consenting of all subjects with the new information.

If the allegation involves research misconduct, the IRB chair will report this to the Dean of the investigator's school, and the UNTHSC Compliance Office.

17.3 Administrative Hold, Suspension, Closure or Termination of IRB Approved Human Subjects Research

Section updated on 11/02/10 (clarification on suspension or termination of all research activities within a department due to one or more non-compliant investigators).

Section updated on 3/30/10 to include procedures for Administrative Holds/Administrative Announcements and clarification on the reporting requirements for IRB Suspension and Terminations. In addition, Section 17.3 and 17.4 were consolidated into one section.

Section updated on 10/6/11 related to Administrative Hold procedures for Continuing Reviews.

Section updated on 03/21/14 related to Administrative Hold procedures for Post-Monitoring Approval Audit.

Section updated on 03/28/14 related to Administrative Hold procedures for Post-Monitoring Approval Audit.

The UNT Health Science Center IRB has the authority to place an administrative hold, closure, suspend, or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. The IRB conducts suspensions, and terminations in accordance with 45 CFR 46.113, 21 CFR 56.108 (b) (3) and 21 CFR 56.113. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, appropriate institutional officials, sponsor, OHRP and/or FDA, and other applicable agencies.

Definitions

Administrative Hold/ Warning: Action initiated by the IRB to place significant research activities on hold temporarily to allow for additional information to be obtained.

Administrative Closure: The IRB via OPHS administratively terminates a research study based on specific circumstances associated with Principal Investigator's failure to provide critical information in a timely manner.

Suspension / Termination of Research Activities/IRB Approval: A directive of the convened IRB, the IRB Chairperson (or designee), to stop some or all previously approved research activities. This directive may be temporary or permanent dependent on conduct of study. Suspension can be applied to such activities as recruitment, enrollment, or specific study procedures. Suspended protocols remain in an "active" status and require continuing review.

Terminated protocols are considered "closed" and will no longer be required to undergo continuing review. The IRB withdraws approval of such research activities.

The OPHS/IRB will report any suspensions or terminations of research activities to the Institutional Official. Additionally, the OPHS / IRB will report to the Sponsor (if applicable), OHRP and/or FDA, and other regulatory agencies as required.

Suspension of Principal Investigator: A directive of the IRB to suspend the privilege of a Principal Investigator to conduct human subject research.

Administrative Hold/Administrative Warning

An administrative hold/warning is not a suspension or termination. Protocols on administrative hold remain open and require continuing review.

The IRB may require the Investigator to place some or all research activities on hold until additional information can be obtained in order to determine if a change in the potential risk/benefit profile has occurred, if a change in the rights or welfare of a participants has occurred or if potential areas of non-compliance exist in a currently approved research protocol. This may occur through various sources including a complaint received by the UNTHSC IRB, an allegation of noncompliance to the IRB, a discovery by the Investigator of potential additional risks, or IRB Chair of convened meeting deliberations. Protocols will be placed on an administrative hold if the Investigator fails to submit a Progress Report/Continuing Review to the Office of Research Compliance in a timely manner, resulting in a lapse in the approval period. An Administrative Hold may also be placed on a protocol as a result of a post-approval monitoring audit. Such a hold may be initiated by the IRB Chair and/or Executive Director, Office of Research Compliance as a result of audit findings that require modifications to protocol or a corrective action plan.

At the time of an audit, the principal investigator may, in writing or via email, voluntarily place the protocol on hold (cease all recruitment and subject interactions) in order to update, modify or amend the protocol and/or related materials to address audit findings.

The IRB will notify the Investigator in writing of the IRB's determination for "Administrative Hold" and the specific requested activities to be placed on hold. At any point, the IRB may require or make recommendations for additional education or compliance interventions for the Investigator and his/her staff through the Office of Research Compliance. If the additional information is evaluated and the IRB Chair or designee determines that no change to the potential risk/ benefit profile has occurred, that the rights or welfare of participants have not been compromised, or that the issue of non-compliance can not be verified or has been properly addressed, the investigator will be notified that the study may return to active status. Otherwise, the issue will be referred to the convened IRB. Administrative holds enacted by the IRB Chair or designee will be reported to and reviewed by the IRB at the next convened meeting.

In addition, no new IRB submissions will be accepted for an Investigator who has an administrative hold/warning until the issue that led to the administrative hold/warning has been resolved.

Administrative Closure

On some occasions, it may become necessary for the IRB via the OPHS to administratively terminate a protocol. Such administrative closure is based on specific circumstances associated with Principal Investigator's failure to provide critical information in a timely manner. In such cases, described below, the protocol will be closed. Such administrative closures may not require reporting to external agencies, sponsors, or federal regulatory agencies. At UNTHSC, administrative closures are authorized by the IRB Chairperson and/or designee. A protocol can be administratively closed by the IRB when one of the following situations occurs:

A) Research where the Principal Investigator fails to respond to conditional approval letters (board action forms) and/or OPHS requested modifications (pre-review findings) in a timely manner (6 months).

New protocol applications or modifications that have received conditional approval pending Principal Investigator response will be closed by the UNTHSC IRB if the researcher fails to respond to the conditional approval letter within **6 months** after the date the conditional approval letter has been sent. This closure may be waived by the IRB Chairperson based on exigent circumstances or a specific written request by the Principal Investigator for additional specific time to complete required modifications.

Procedure:

- Prior to administrative closure, a final notice regarding imminent closure will be sent via email to the Principal Investigator.
- Unless an extension is granted by the IRB Chairperson, a "Notice of Administrative Closure" letter (see Appendix F) will be sent to the principal investigator and his or her designee if appropriate. The date of the letter will be the effective date of closure. The protocol will be considered closed. Note that, since the protocol was never actually activated, there is no human subject risk management issue associated with this type of administrative closure.

B) Research protocol in which the Principal Investigator fails to respond or provide adequate documentation for continuing review within 3 months (90 days or more) after IRB approval has lapsed.

All IRB-approved protocols involving human subjects require continuing review. If adequate documentation has not been provided in time for a continuing review, and the IRB cannot approve the protocol, then that protocol approval period expires and the protocol is placed on administrative hold (see above).

As stated in federal regulations, *enrollment of new subjects cannot occur after the expiration of IRB approval*, except in cases where continuation is essential for subject safety and well-

being, as determined by the IRB chairperson and until effective continuing review can be conducted and approval be granted.

However, if there is a significant delay in providing information needed for an effective formal continuing review, the protocol may be administratively closed by the IRB (unless there are subject safety and welfare concerns and/or the closure is waived by the IRB Chairperson). Note that regulations and UNTHSC IRB policy do not allow researchers to continue to engage in research once a lapse (expiration) in IRB approval occurs. *Enrollment of new subjects cannot occur after the expiration of IRB approval.*

Procedure:

- Prior to administrative closure a final notice regarding imminent closure will be sent via email to the Principal Investigator.
- Unless an extension is granted by the IRB Chairperson, a Notice of Administrative Closure letter (see Appendix F) will be sent to the principal investigator and his or her designee if appropriate. The date of the letter will be the effective date of closure. The protocol will be considered closed.
- If the researcher wishes to continue with the administratively closed project, an entirely new IRB application must be submitted to the IRB for review and approval, along with a letter of explanation and Corrective And Preventative Action plan to avoid such lapse in providing required information to the IRB needed for the earlier continuing review.

C) Inactivation due to non-enrollment if, during a continuation review, the principal investigator reports that no new subjects have been enrolled in the preceding period of two or more years.

If, during a continuing review, the principal investigator reports that no new subjects have been enrolled for a period of two or more years, the protocol may be administratively closed by the IRB. In this event, the IRB may either consider administrative closure of the study, or request additional information from the Principal Investigator to justify continuation. If administratively closed, that closure will constitute a Final Report.

D) Research where the Principal Investigator has left the institution and did not notify the IRB (or amend the protocol by replacing themselves with a new Principal Investigator) within 3 months (90 days) after his/her departure.

If OPHS has been notified or has determined that the Principal Investigator has left the institution or is no longer otherwise affiliated with UNTHSC the protocol will be administratively closed within **1 month (30 days)** unless:

1. the PI has previously notified the IRB and designated a new (replacement) PI, or
2. the Department Head of the PI's department agrees to act as Principal Investigator or delegates someone else to serve as PI, and provide all relevant and appropriate information suitable for continuing review and oversight

Procedure:

- Prior to administrative closure a final notice regarding imminent closure will be sent via hard copy and email to the Principal Investigator's unit/department chairperson.
- If the department chairperson does not become the PI of record or designate someone else to serve as PI of record, a dated administrative closure letter (hard copy) will be mailed to the Department/Unit head as well as an email attachment. The date of the letter will be the effective date of closure. The protocol will be considered closed.

E) Other Administrative Closure Situations

Occasionally, there may be other circumstances that will result in administrative closure of a protocol. In this case, notice of imminent closure will be sent to the appropriate party as described above, and the specific reason for the administrative closure will be cited in the "Notice of Administrative Closure" letter that will be sent to the investigator.

Multiple protocol administrative closures by a single investigator

Principal Investigators are required to manage their protocols involving human subjects and to plan accordingly for timely and effective continuing reviews, final reports, transfer of PI status and other essential protocol and document management tasks. Repeated need for external (i.e. administrative) intervention and/or closure indicates a potential problem with good research management practices.

If two or more studies involving a single Principal Investigator are administratively closed within a 2-year period, the IRB Chair may initiate a "for-cause" audit of all projects involving that researcher to review the circumstances and make recommendations to a convened IRB the regarding possible corrective action that may be required.

Suspensions and Terminations:

The IRB, through OPHS, promptly notifies the investigator, in writing, of all suspensions or terminations of IRB approval. The notification letter includes the following:

- Identifies the suspended or terminated research.

- Includes a statement of the reasons for the IRB's action;
- Requires the investigator to submit to OPHS for IRB review, the proposed procedures for withdrawal of currently enrolled subjects that considers subject rights and welfare. The IRB then reviews the proposed procedures at a convened meeting. The IRB may require oversight or may transfer responsibility to another investigator to ensure implementation of these procedures;
- Requires the investigator to submit to OPHS for review by the IRB a proposed script or letter notifying all currently enrolled subjects that are affected by the suspension or termination. The IRB reviews the proposed script or letter. If follow up with subjects for safety reasons is permitted/required by the IRB, subjects *must* be so informed. The OPHS or the IRB may directly contact subjects to effect this notification; and
- Requires the investigator to report to the IRB or sponsor, on an ongoing basis, any events that would have required reporting had the former subjects continued to be enrolled in the research. The IRB may require oversight or may transfer responsibility to another investigator to ensure implementation of these procedures.

Investigators who fail to comply with IRB directives or federal or state law or regulations may be subject to administrative action by the University.

The convened IRB, IRB Chair, or Director, OPHS are authorized to suspend or terminate IRB approval for research. If there is an urgent situation requiring protocol suspension or termination of a study, the IRB Chair, Vice Chair or Director, OPHS may make this determination. Any protocol approval that is terminated or suspended is reported to the convened IRB at the next IRB meeting.

In the event that a UNTHSC department has one or more investigators (faculty/staff) who are not compliant with IRB directives and/or federal and state regulations, the IRB may determine a state of non-compliance and direct that all research activities within that department be subject to administrative hold or compliance review. Such actions may be made by the IRB Chair (who will then report it at the next convened meeting of the IRB) or by the convened IRB.

Examples of Actions that May Cause Suspensions or Terminations of IRB-Approved Protocols

- Inappropriate involvement of human subjects in research;
- Inhibition of the rights or welfare of participants;

- Serious or continuing noncompliance with federal regulations or IRB principles and procedures; or
 - New information regarding increased risk to human participants, etc.;
- or*

Handling Suspension of IRB Approval and Procedures by which a Study's Approval Status May Be Changed & Subsequently Reinstated:

OPHS Staff Responsibilities

The OPHS staff notifies the PI in writing of IRB determinations. The letter requires a signature of the IRB Chair or his/her designee. The OPHS staff assists the board in obtaining information from the investigator and completes a directed audit and/or develops a Corrective and Preventative Action plan as deemed appropriate by the IRB Chair. OPHS staff is available as a resource to the investigator, and notifies the appropriate persons regarding any suspensions of IRB approval.

Investigator Responsibilities

Research activities cease, as specified in the suspension criteria, until the investigator is notified that the full IRB has granted approval for the study to resume. It is within the authority of the IRB to terminate the study. The investigator complies with all Corrective and Preventative Action plans required by the IRB. The investigator notifies the sponsor (if there is one) when the UNTHSC IRB has suspended, terminated, or reinstated the research (note that this reporting is not necessarily required for administrative closures, only in the case of research not being conducted per federal regulations or associated with unexpected serious harm to subjects. The investigator is responsible for notifying all affected subjects of the suspension. In the case of clinical trials, the terms of the contract with the sponsor will prevail. The Office of Clinical Trials will assist the investigator with this notification. The investigator submits the script or letter of notification (to subjects) to the IRB for approval prior to notification of research subjects. The investigator continues to report to the IRB adverse events, unanticipated problems involving risks to subjects or others, and serious or continuing noncompliance with federal regulations or IRB requirements or determinations.

IRB Committee Responsibilities

The IRB may suspend approval of any or all research activities. Before suspending IRB approval, the IRB or individual requesting the suspension must consider whether any actions are necessary to protect the rights and welfare of currently enrolled subjects (e.g., allowing subjects to continue in the research, transferring subjects to other investigators, transferring subjects to physicians to be provided clinical care off protocol, and monitoring of current or former subjects).

A convened meeting of the IRB reviews the study and determines whether circumstances warrant suspension of IRB approval. Some examples of situations that may warrant suspension are:

- Falsification of study safety data;
- Failure to comply with prior conditions imposed in writing by the IRB;
- Repeated or deliberate failure to obtain or document informed consent from human subjects:
- Repeated or deliberate omission of a description of serious risks of the research intervention when obtaining informed consent; and/or
- Repeated or deliberate failure to provide informed consent in a language understandable to the subject;
- Repeated or deliberate failure to comply with conditions placed on the study by the University, IRB, sponsor, or FDA or other governmental agency;
- Repeated or deliberate failure to obtain prior review and approval of changes to an approved protocol(s) by the IRB;
- Repeated or deliberate failure to follow the signed Investigator statement or protocol, e.g., by enrolling subjects who do not meet inclusion *criteria* or *who do not meet exclusion* criteria;
- Repeated or deliberate failure to maintain accurate study records or submit required adverse event reports to the IRB;
- Repeated or deliberate falsification, fabrication, or concealment of study records, e.g., by substituting in study records the results of biological samples from subjects who met the inclusion criteria for samples of subjects who did not meet the inclusion criteria, or by fabricating participants.

The IRB may request an ad hoc review from an independent source with expertise in the type of research being conducted or expertise in the specific area of concern. The IRB may request the development of a Corrective and Preventative Action plan and/or the completion of a directed audit by the OPHS compliance auditor or designee.

The IRB notifies the investigator in writing of its decision to suspend the study and provide a rationale for its actions. This letter includes an opportunity for the PI to respond to the Board's determinations and to attend an IRB meeting to discuss the suspension and provide clarification of the issues.

Suspensions of IRB approval are reinstated for approval after corrective actions are completed to the IRB's satisfaction. The Board may approve the study with or without additional restrictions (e.g., mandating a data and safety monitoring committee to oversee the research at designated intervals, increase in the frequency of IRB review, observation of the consent process).

Handling Termination of IRB Approval and Procedures :

OPHS Staff Responsibilities

The OPHS Director and/or staff designee notifies the PI in writing of IRB determinations. The letter requires a signature of the IRB Chair or his/her designee. OPHS promptly notifies the appropriate persons regarding any suspensions of IRB approval.

Investigator Responsibilities

The investigator ceases all study-related activities and, according to the terms of the contract, notifies the sponsor of the termination of UNTHSC IRB approval. The investigator is responsible for notifying all affected subjects of the termination. The Office of Clinical Trials will assist the investigator with both sponsor and subject notification for applicable studies. The investigator submits the script or letter to the OPHS and IRB Chair for approval prior to notification of participants. Adverse events, unanticipated problems involving risks to subjects or others, and serious or continuing noncompliance with federal regulations or IRB requirements or determinations will continue to be reported to the IRB.

IRB Committee Responsibilities

The IRB reviews a study for termination of IRB approval at a convened IRB meeting. Before termination of IRB approval, the IRB or individual requesting the termination must consider whether any actions are necessary to protect the rights and welfare of currently enrolled subjects (e.g., allowing subjects to continue in the research, transferring subjects to other investigators, transferring subjects to physicians to be provided clinical care off protocol, and monitoring of current or former subjects). The Board may request an ad hoc review from an independent source with expertise in the type of research being conducted or expertise in the specific area of concern. The IRB notifies the investigator in writing of the decision to terminate the study and provide a rationale for its actions. This letter includes an opportunity for the PI to respond to the board's determinations and to attend an IRB meeting to discuss the termination and provide clarification of the issues.

All suspensions or terminations of IRB approval are promptly reported in accordance with IRB policy.

The institution may determine that suspensions or terminations associated with a particular study or an investigator are repetitive and / or serious and warrant action for issues of serious and continuing noncompliance.

17. 4 Reporting Requirements (Unanticipated Problems Involving Risk to Subjects or Others, Serious or Continuing Noncompliance, and Suspensions or Terminations)

Section number changed from 17.5 to 17.4 on March 30, 2011 because of the consolidation of Sections 17.3 and 17.4.

The following will be reported in accordance with this policy and procedure:

1. Any unanticipated problem involving risks to subjects or others;
2. Any serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB; and
3. Any suspension or termination of IRB approval.

Report Content

OPHS staff drafts a report for unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspension or terminations. The report includes the following information:

- Title of the research project and/or grant proposal that was suspended or terminated;
- Name of the principal investigator on the protocol;
- Number of the research project assigned by the IRB that was suspended or terminated and the number of any applicable federal award(s) (grant, contract or cooperative agreement) *and/or sponsor's protocol descriptor*;
- Sponsor name and date reported to Sponsor
- A detailed description of the reason for the suspension or termination; and
- The actions the institution is taking or plans to take to address the problem, noncompliance or suspension or termination.

Drafting Process

OPHS staff forwards the draft report to the IRB Chair or designee and incorporates their suggested revisions as appropriate. The IRB Chair or designee then forwards the draft report to the Institutional Official (IO). The IO may consult with Legal Affairs, but will work out the

language of the final report with the IRB Chair or designee to ensure that it includes all of the required elements as described above.

Once the report is finalized, the IO signs it and returns it to the IRB Chair or designee for distribution.

Distribution

The IRB Chair or designee, when appropriate, submits the report to:

- OHRP, if federally funded
- FDA, when the research is subject to FDA regulations
- Funding agency, if required by federal regulation, contract, or other agreement
- Institutional Official (if federally funded or not)
- Principal Investigator
- Department Chair, institute director, and/or PI's supervisor
- Grant and Contract Management (GCM) (only if determined by the IRB leadership to merit reporting to GCM)
- Non-federal study sponsor (only if determined by the IRB leadership *in consultation with the Office of Clinical Trials* to merit reporting to the sponsor)
- Leadership of any other institutional committee or entity involved in the oversight of the research (e.g., IBC, Office of Compliance, etc.).

Timeline

Reports are to be distributed to all parties within 45 days from:

- The day the convened IRB determines that an incident represents an unanticipated problem involving risk to subjects or others;
- The day the convened IRB determines that an incident represents serious or continuing noncompliance; or
- The day the convened IRB votes to suspend or terminate a study.

- For more serious incidents, reports *will* be distributed within *the regulatory agency(ies) required time periods* from the time at which the above determinations are made.

Filing

Copies of all reports made in accordance with this policy and corresponding responses are maintained in an appropriate file located within OPHS.

17. 5 Reporting Protocol Violations

Section number changed from 17.6 to 17.5 on March 30, 2011 because of the consolidation of Sections 17.3 and 17.4.

Protocol Violations

Protocol violations are considered to be any change or departure (i.e. “deviation”) from the study design or study procedures of a research protocol that affects the subject’s rights, the potential risk/benefit ratio of the study, the safety or well-being and/or the integrity (completeness, accuracy or reliability) of the study data. Essentially, a protocol violation is a deviation from the “flight plan” of the protocol itself.

In many cases, protocol deviations that will be defined as violations will fall into one of the following 5 categories:

1. The violation has harmed or posed a significant or substantive risk of harm to the research subject.
2. The deviation has compromised the scientific integrity of the data collected for the study.
3. The deviation is a willful or knowing breach of human subject protection regulations, principles, or procedures on the part of the investigator(s).
4. The deviation involves a serious or continuing noncompliance with federal, state, local, or University human subject protection regulations, principles or procedures.
5. The deviation is inconsistent with the University’s Human Research Protection Program’s (HRPP) research, medical, or ethical principals.

The following are examples of protocol violations (this list is not intended to be exhaustive). Note that any of these actions is a protocol violation:

- Variations or errors in drug dosing/dispensing/storage
- Use of prohibited (concomitant) medications (*by a subject*)

- Enrolling subjects who *do* not meet the inclusion/exclusion criteria (that is NOT related to screen failures)
- *Continued participation of a research subject who has* met withdrawal criteria during the study but was not withdrawn
- Unauthorized (i.e. not IRB Approved) persons (faculty, staff, students, residents, etc.) participating in the conduct of a research study
- Premature “unblinding” of research treatment or data
- Loss or corruption of samples and/or data
- Failure to obtain informed consent prior to initiation of study procedures or inadequate or improper consenting of human subjects
- Use of an unapproved or expired consent document, oral consent procedure, *or test article*
- Incorrectly performed or missing protocol-required tests and procedures
- Incorrect handling of biological samples
- Changing the protocol without prior IRB approval
- Falsifying research or medical records
- Performing tests or procedures beyond the professional scope or privilege status (credentialing)
- Breach in confidentiality
- Failure to submit Data Safety Monitoring Board (DSMB) reports to OPHS in a timely manner *if* such a report has been required/requested by the IRB (see section 18.4 “Submission of DMSB Reports to OPHS” for policy).
- Failure to report unanticipated problems involving risks to subjects or others, and adverse events (serious and/or unexpected) in a timely manner (see section 7.4 “Defining and Reporting Unanticipated Problems Involving Risks to Subjects or Others, and Serious Adverse Events” for policy)
- Protocol violations identified by sponsor monitor visits, or study coordinator that may affect the safety of the participant or the integrity of the study data.

Protocol violations should be reported to OPHS within 10 working days of discovery. This report must use the appropriate procedures described below.

For Clinical Trials:

- A letter, signed by the Principal Investigator, must be submitted which contains the following information:
IRB Project #, Subject ID #, Date(s) of the Event(s)
- Description of the protocol violation
- How the event deviated from the protocol
- Date the study sponsor was notified of the violation
- Investigator's assessment regarding any effect on subject risk as a result of the violation. Include a description of additional treatment the subject required as a result of the violation.
- Corrective *and preventive* action plan describing what will be implemented in order to avoid the violation from reoccurring in the future.

If applicable, please also submit supporting documentation from the study sponsor.

For Non-Clinical Trials:

Investigators should complete and sign the "Protocol Violation Reporting Form" (see Appendix C) and submit the form to OPHS for review. Submission of this form does not preclude additional investigation or inquiry by OPHS or the IRB.

Protocol Deviations

Protocol deviations are considered to be those changes or alterations in the conduct of the study which do not have an impact on the subject's rights, safety, or well-being or completeness, accuracy, or reliability of the study data. The following are examples of protocol deviations:

- A minor variation in clinic visits/follow up (e.g. "Day 10 visit" *was outside of the specified "window" for that study visit*) if no protocol medication, treatment, or supervision is missed.
- Collection of study data (e.g. temperature reading) performed incorrectly by subject or subject's parent/guardian
- Changes in the formatting of an IRB approved study questionnaire (for example: font size, font face, margins, etc)

The OPHS/IRB does not require that protocol deviations be reported by the investigator. However, if the study sponsor requires that the deviation be reported to the IRB, the IRB will provide acknowledgement of receipt and review of the deviation. In any case, investigators should contact OPHS staff for guidance in determining if a deviation should be reported as a protocol violation if they are unsure.

Guidance for Avoiding Protocol Violations and Deviations

The Principal Investigator is the responsible party and will be held accountable for the conduct of the study. There are some steps that investigators can take to prevent or reduce the likelihood of protocol violations and deviations occurring during the conduct of their study. Here are several recommendations:

- It is important for all study personnel to be familiar with the protocol and understand their role in the study. The Principal Investigator should make sure that the delegation of tasks is well understood by the study personnel.
- Researchers should plan *for* protocol violations *that* might occur during the study, and *should* have an agreed upon procedure for discussing and reporting protocol violations. For example, it is important to understand what type of documentation will be required by the sponsor, determine who will notify the IRB of a violation, and determine what course of action might be taken to prevent protocol violations.
- Prepare study amendments in a timely manner and submit them to OPHS for IRB review before implementing the changes.
- Ensure that Serious Adverse Event (SAE) are submitted to OPHS in a timely manner.
- If DSMB reports are required by the IRB, ensure that such reports are submitted to OPHS in a timely manner.
- Ensure all subjects are properly consented before initiating any study procedures and if required, re-consent each subject as the study proceeds and new information becomes available
- Ensure that all key personnel working on a study are IRB approved to do so.
- Ensure that the Principal Investigator and research team are familiar with the Guidance on *Good Clinical Practice (GCP) as well as* OHRP and FDA regulations pertaining to research with human subjects.

Chapter 18: Data Safety Monitoring (DSM)

CHAPTER CONTENTS

- Data Safety Monitoring (DSM)
- Data Safety Monitoring Board (DSMB)
- The Relationship Between DSMBs and IRBs
- DSMB Reports

Background

The UNTHSC IRB follows the Department of Health and Human Services (HHS) and the U.S. Food & Drug Administration (FDA) regulations regarding the monitoring of research for the safety of human subjects. This chapter describes situations in which a plan for the monitoring of research is required to protect human subjects, the roles of Data Safety Monitoring Boards (DSMB: also called Data Monitoring Committees, DMC), and the relationship between DSMBs and IRBs.

18.1 Data Safety Monitoring (DSM)

The regulations give criteria for study approval: "when appropriate, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects" 45 CFR 46.111[a][6]. It is not practical or feasible for an IRB to directly monitor the data involved in all studies involving human subjects. However, it is appropriate for the IRB to rely on the input of such monitoring systems and committees.

The IRB is responsible for enforcing and determining when a study needs ongoing monitoring by a DSM plan or the establishment of a data safety monitoring board (DSMB) to ensure protection for research subjects.

Every clinical trial conducted at UNTHSC must describe a plan for safety and data monitoring, or otherwise justify not having such a committee in place.

Specific plans will be based on:

- The amount of risk involved for participating subjects;
- The size and complexity of the clinical trial;
- The nature of the investigational agent;
- The study sponsor; and
- The phase of the clinical trial.

DSM plans can be required for non-clinical trials and for studies involving more than minimal risk as determined by the Board.

During the initial protocol approval process and annual review, the IRB will review all proposed protocols for scientific relevance, protocol completeness and the presence of an appropriate DSM plan, if required.

Low to medium risk studies will develop a DSM plan based upon the characteristics of the individual study. Investigators must describe how the study will be monitored for the safety of subjects and for the validity and integrity of the data.

18.2 Data Safety Monitoring Board (DSMB)

A DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if study continuation is scientifically and ethically appropriate.

Factors that Suggest a DSMB Is Needed

- A large study population;
- Multiple study sites (it is more difficult to recognize a pattern of increased or unusual problems when investigators treat small fractions of the population separately);
- The study is blinded;
- The study employs high-risk interventions that may include highly toxic therapies or dangerous procedures, expected high rates of morbidity or mortality in the study population, or high chance of early termination of the study; and/or
- The study includes vulnerable populations, such as minors, prisoners, and/or pregnant women.

18.3 The Relationship between DSMBs and IRBs

The National Institutes of Health (NIH) policy, available via hyperlink below, explicitly identifies required communications that must occur between DSMBs and IRBs ("Guidance on reporting adverse events to IRBs for NIH-supported multi-center clinical trials," dated June 11, 1999 <http://grants.nih.gov/grants/guide/notice-files/not99-107.html>). The DSMB should provide feedback at regular and defined intervals to IRBs. After each meeting of the DSMB, the DSMB's Executive Secretary or Chair should send a brief summary report to each investigator. The report should document that a review of data and outcomes across all centers took place on a given date. It should summarize the DSMB members' review of the cumulative toxicities reported from all participating sites without specific disclosure by treatment arm. It should also inform study investigators of the DSMB members' conclusions with respect to progress or need for modification of the protocol. The investigator is required to transmit the report to their local IRB.

The IRB then follows guidelines set out by the National Cancer Institute (NCI), as they are the most comprehensive of the NIH guidelines. NIH's NCI model states that "All clinical trials supported or performed by NCI require some form of monitoring." Risk and complexity are identified as the most important determinants of the degree and method of monitoring.

Early studies (non-therapeutic, Phase I, Phase II) are allowed great flexibility in monitoring, and it is specifically required that the Principal Investigator (PI) do the monitoring. However, the policy requires written principles and procedures, and also requires that "regardless of the method used, monitoring must be performed on a regular basis. The IRB may require establishment of a DSM committee for Phase I and II trials if the studies have multiple clinical sites, are blinded, or employ high-risk interventions or vulnerable populations.

All Phase-III studies require a formal DSM plan, which may mean the establishment of a DSMB at the sponsoring institute, at the study site or at the lead institution of a multi-center trial. DSM activities for each study will continue until all patients have completed treatment and are beyond the time point(s) at which study-related adverse events would presumably be encountered.

18.4 Submission of DSMB Reports to OPHS

All DSMB reports should be submitted to the OPHS/IRB within **10 working days** of receipt by the Principal Investigator.

Additionally, a copy of the most recent DSMB report should be submitted with the Progress Report Application (continuing reviews and final reports). Additionally, copies of any executive summaries of the data safety committee or multi-center trial reports should be included in the continuing review packets for review by the Board (see Section 5.4 for specific information on the number of copies).

Investigators will be asked to list the date of the most recent DSMB meeting/ report in the Progress Report Application.

Chapter 19: Complaints, Concerns and Appeals Regarding Human Subjects Research

CHAPTER CONTENTS

- Subject Complaints
- Complaints from IRB Reviewers/Designees Regarding Undue Influence
- Complaints Regarding the IRB, or Aspects of the Non-IRB HRPP
- UNTHSC Ethics Hotline
- Investigator Appeal of IRB Action

Overview

The principles and procedures addressed in this chapter briefly delineate the different kinds and sources of Human Research Protection Program (HRPP) complaints, concerns and appeals regarding research projects as well as OPHS and/or IRB findings and determinations and actions to be taken to resolve them. Attempts to impede the independence of the IRB are also included in this policy.

19.1 Appeals Regarding Human Subjects Research

This policy recommends seeking redress of the complaint or appeal through the nearest organizational entity, although a complainant or recipient must exercise judgment about whether to address the complaint locally or redirect it to a more appropriate person or office. Maintaining objectivity and confidentiality is a key determinant in directing a complainant/complaint. The most immediate level of contact to the complainant may not be able to provide the expected level of objectivity and confidentiality.

Subject Complaints

Subjects in a research project may observe or be involved in a breach of research ethics or human subject rights. Written informed consents and fact sheets provide information to subjects about how to handle such issues and whom to contact (researcher or IRB) as required by regulations. Subjects may also call the UNTHSC Ethics Hotline at 1-877-606-9187 (see below for more detail on this Ethics Hotline).

Regulations require that contact information be provided to subjects for the researcher/research team and IRB. Also, at UNTHSC, the Office for the Protection of Human Subjects (OPHS) is an appropriate place to voice concerns.

Once a subject complaint is received, the IRB/OPHS office will attempt to substantiate the complaint. This process involves reviewing the study in which the subject is enrolled to ensure that the study has received and maintains active IRB approval and ensure compliance with pertinent federal and state regulations. The IRB/OPHS office may contact the Principal Investigator (PI) and/or research staff for additional information to assist with the validation and/or dismissal of the complaint. Once all the information is received, the IRB/OPHS will determine if any further action is necessary. The IRB/OPHS will then provide written correspondence to the subject and PI with their determination and justification for actions taken.

If the IRB/OPHS office suspects there may be potential non-compliance, the OPHS will initiate the process as outlined in the policy on handling allegations of non-compliance.

Complaints from IRB Reviewers/Designees Regarding Undue Influence

Any OPHS staff member, IRB member, or other individual involved in the review of research, who believes they have been the target of undue influence by an investigator or other individual should report the incident to the OPHS Director or IRB Chair.

The entity/individual receiving this report will attempt to validate the allegation and forward the validated allegation to the FWA Institutional Official as well as Office of Compliance, where corrective action will be determined.

Complaints Regarding the IRB, or Aspects of the Non-IRB HRPP

Subjects/participants, researchers, IRB members, and others who have human subjects research related complaints, concerns, recommendations, or reports of violations are encouraged to contact one of the following offices listed below. Aspects of the HRPP unrelated to the IRB may also be directed to these offices. All inquiries are taken seriously and will be directed to the appropriate personnel. When a complaint, concern, recommendation, or report of violation made to any one of the offices listed below reveals the need to consider modifying any aspect of UNTHSC's Human Research Protection Program, due consideration will be given and changes made as appropriate.

Complaints regarding the IRB or aspects of the non-IRB HRPP should be made to the nearest organization entity independent of the IRB. This could be the OPHS, Office of Compliance, the Vice President for Research (UNTHSC FWA Institutional Official). Attempts to get adequate information to validate the circumstances of the complaint will be sought by one or all of these entities.

UNTHSC Ethics Hotline

The UNTHSC Office of Institutional Compliance Ethics Hotline is a “hotline.” It is a toll free number used to report allegations of fraud, theft, waste, non-compliance, and abuse at UNTHSC. Anyone can call the line (student, faculty, staff, patient, research subject or visitor). The Ethics Hotline encourages the reporting of suspected waste, fraud, or abuse; however anyone who has knowledge that an applicable law, regulation, or UNTHSC policy has been violated should report such information.

The Ethics Hotline is available 24 hours a day, 365 days a year and anonymity is guaranteed. Callers do not have to identify themselves.

The Ethics Hotline toll free number is 1-877-606-9187.

More information about the Ethics Hotline can be found at the following link:

<http://www.hsc.unt.edu/departments/Compliance/>

Investigator Appeal of IRB Action

Per federal regulations [45 CFR 46.109 (a)], the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all proposed research activities. The investigator will be notified in writing of the IRB’s decision. An investigator may appeal the revisions required by the IRB. This appeal should be in writing and submitted to the Director of OPHS who will enter it into the protocol file and forward to the IRB Chair. All appeals will be reviewed by the convened IRB at the next available meeting.

An investigator may also appeal the IRB's decision to disapprove a research protocol. However, an IRB decision can only be appealed back to the convened IRB; no one at the University (including the Dean, Vice President, etc.) may over-turn a convened IRB or IRB Chair’s finding(s) or determination(s). The appeal must be in writing and may also be presented in person to the convened IRB, and will be reviewed by the Full Board at a convened meeting. Investigators will be notified in writing of the Board’s decision related to the appeal; again, this IRB decision regarding revisions or disapproval is final and by federal regulations, cannot be reversed or overridden by another party.

Note, that an IRB approval of a research project does not assure that the project will go forward. IRB approval only states that a project meets federal regulations for research conducted on human subjects and can be undertaken in accordance with those regulations. However, other UNTHSC officials may determine that an IRB-Approved project cannot be

conducted (institutional concerns regarding facilities, resources, mission-orientation, etc.). In these situations an IRB determination of “Approval” can be over-ridden or reversed by another party.

Chapter 20: North Texas Regional IRB Compliance Audit Principles and Procedures

Compliance Audit Principles and Procedures were updated/revised on May 1, 2018.

Overview

This section describes policy and corresponding procedures establishing a mechanism for conducting two categories of oversight compliance audits: periodic compliance audits (also known as “post-approval monitoring (PAM) audits” and directed (for-cause) compliance audits on research projects that involve human subject research at the University of North Texas Health Science Center (UNTHSC (NTR IRB).

Federal Regulatory Basis:

The Office of Research Compliance via the North Texas Regional Institutional Review Board is responsible for oversight of approved protocols of human subject research based on regulation and policy found in Title 45 Code of Federal Regulations Part 46, Title 21 CFR Parts, 56 and ICH Good Clinical Practice Guidelines as adopted by the FDA, the US Federal-wide Assurance and University policy.

45 CFR 46.109 (e) and 21 CFR 56.109 (f) IRB review of research, reads “.....shall have authority to observe or have a third party observe the consent process and the research.”

Policy:

In order to assess compliance with IRB approved protocol, state and federal laws, and IRB principles and procedures, periodic compliance audits and directed compliance audits of research projects involving human subjects will be conducted by the research compliance auditor or designee and reported to the North Texas Regional Institutional Review Board (NTR IRB).

Chapter 20 of this Standard Operating Procedure apply to all human subjects research including exempt, expedited, and full review protocols reviewed and approved by the North Texas Regional IRB.

20.1 Periodic Compliance Audits

All on-going human research projects with IRB approval granted by the NTR IRB are eligible to be audited by the research compliance auditor or designee. For the most part, these post-approval audits are considered routine and “not for cause” audits. Such audits are intended to be proactive and focused on educating investigators and research staff about their ethical and regulatory responsibilities regarding human subject research.

20.2 Directed Compliance Audits

Directed compliance audits will be initiated by the Office of Research Compliance/ NTR IRB as a result of a complaint, suspected non-compliance, or questions/concerns regarding the safety and welfare of research participants enrolled in a research study.

20.3 Selection of Protocols for Audit

The Research Compliance Auditor or designee will perform periodic routine and “for cause” directed audits to ensure compliance with the approved IRB protocol, federal and state regulations, as well as NTR IRB policies associated with the protection of research participants. Protocols can be selected on a random basis from any categories of review: exempt, expedited, or convened meeting (“full board”). Selection of a protocol for audit does not imply any suspected noncompliance for routine audits. A risk-based selection process may be utilized or randomly selecting approved protocols reviewed by either expedited or full board procedures (see section 20.4).

Investigators are informed in advance of the impending audit, informed of the process, and the type of records to make ready for review (see sections 20.5 & 20.6). With the cooperation of the principal investigator, it is expected that a routine audit can be conducted, in most cases, in 1 to 5 days or less.

20.4 Criteria for Compliance Audit selection

The Office of Research Compliance / NTR IRB may use any one or more of the following criteria for selection of a research project for compliance audit:

- At random
- At the discretion of the IRB
- Risk based selection: high risk studies as designated by the IRB; studies that include vulnerable populations (i.e. pregnant women, children, prisoners, etc.); studies reporting on-site SAEs or protocol violations; studies reporting a high local-site proportional enrollment relative to overall

study enrollment; or Investigators who have limited or no prior research experience with human subjects

- To verify compliance: For those studies in which the Investigator(s) have a previous non-compliance history or concern, or for protocols involving Investigators who have prior FDA 483, “Inspectional Observations”, and / or FDA Warning Letter(s) on file; report of suspected non-compliance or complaint; Previous suspension of the research protocol (for any reason)
- Research placed on administrative hold or closure by the IRB due to failure by the Investigator to submit a study for continuing review or failure to respond to a request for information from the IRB
- To verify Continuing Review reports (Progress Reports)

20.5 Documents / Processes that may be selected for review include, but are not limited to:

- Examination of the protocol and amendments, consent documents, source documents, case report forms (CRF), adverse events, advertisements, recruitment materials, and other research study related documents and correspondences.
- Regulatory submissions and correspondences with IRB, Sponsor, Monitor, etc.
- Review of subject enrollment log and recruitment practices, as needed
- Key personnel training records and site signature / responsibility log
- Review of research data, data collection tools, and procedures
- Review of serious adverse event reporting
- Examination of consent forms to verify that they are signed and dated correctly
- Examination of proper storage, maintenance, and accountability of study related items (i.e. regulatory files, IRB files, subjects’ research and medical records, clinical materials, computer files, electronic data records and storage, specimens, drugs, devices, equipment, and results of procedures and tests performed during the course of the research, etc.)
- Contacting research participants either during or after their participation in research activities to evaluate their involvement in the research study, and/or,
- Observation of the consent process
- Observation of research interactions/interventions with research participants

- Monitor conflict of interest concerns to ensure that the consent document includes appropriate language and disclosures
- Other relevant research project documents or activities as deemed appropriate by the Office of Research Compliance and/or NTR IRB

20.6 Audit Process

1. The research compliance auditor or designee will schedule compliance audits of previously IRB-approved research studies.
2. Prior to initiation of a compliance audit, the principal investigator (PI) will be notified by the research compliance auditor and/or designee at least 10 working days in advance, by email, telephone (including voice mail), or by hard copy letter, that a compliance audit will be conducted. Once the PI has had time to receive the notice of compliance audit (NOA), the research compliance auditor or designee will finalize the date and time of the compliance audit by phone or email confirmation with the PI, or their designee.
3. If the PI fails to respond to the initial NOA for any audit within 5 work days, a follow-up email will be sent to the PI requesting verification of date of audit and location of audit. If the PI fails to reply to the follow-up NOA email, the Principal Investigator and applicable protocol(s) will be referred to the next convened meeting of the NTR IRB for review and consideration. The NTR IRB may request a for-cause audit to be conducted and/or suspend the Principal Investigator's protocol(s) as deemed appropriate. In addition, the IRB Chairperson may exercise his/her authority to notify applicable institutional and other agency official(s) of the PI's failure to comply with NTR IRB policies and procedures.
4. The notice of compliance audit will identify the PI and the protocol to be reviewed during the on-site compliance audit. The research compliance auditor or designee will make every effort to be available via email/phone if the PI has more specific questions as to the nature and/or procedures of the compliance audit.
5. For a directed compliance audit only, in the interest of subject safety, there may be no pre-notification or minimal notification of a compliance audit at the discretion of the *Executive Director, Research Compliance*. However, it is the intent of the Office of *Research Compliance* to inform the PI whenever a directed compliance audit is being implemented.
6. The PI need not be present for the compliance audit; however, either the PI or other study personnel associated with the project being reviewed should be available on-site during the audit. If the PI will not be present for the compliance audit, a designated member of the research staff knowledgeable about the conduct of the study must be available to provide access to study records and to answer questions by the research compliance auditor or designee.
7. Prior to conducting the compliance audit, the research compliance auditor or designee will review the research study file maintained in the Office of Research Compliance to familiarize himself/herself with the IRB application, protocol synopsis, consent forms,

- amendments, including (if applicable) correspondence from the sponsor, monitor, and/or other regulatory/federal agencies, etc.
8. During the compliance audit, the research compliance auditor or designee will have access to all pertinent study documents, records, processes, etc. Please refer to Section 20.5 above, which provides a partial list of the items that may be subject to review during the compliance audit. The research compliance auditor or designee will document compliance audit findings on the *Post Approval Audit Checklist* form.
 9. After completion of the compliance audit, the research compliance auditor or designee will prepare the *Post Approval Monitoring Checklist* form and written memorandum and submit it to the Executive Director, Research Compliance for review. If the audit reveals non-compliance, then a close-out meeting will be scheduled with the PI or designee, Executive Director of Research Compliance or designee, and IRB Chair or designee to formally review the audit findings and discuss a compliance plan to ensure compliance.
 10. Following the audit close-out meeting the PI will receive the final audit memorandum via docu-sign for signature and written response. Following receipt of the *Post Approval Monitoring Checklist / Memo*, the PI will have 15 working days to sign and respond, in writing, to the compliance audit report findings. If comments, acknowledgements, and/or clarifications by the Principal Investigator are not submitted within 15 working days to the Office of Research Compliance, a follow-up email will be sent to the PI requesting the signed report and/or written compliance action plan.
 11. If the PI fails to respond to the follow-up email requesting the signed report and/or written compliance action plan, then the applicable protocol and PI will automatically be brought before the next IRB convened meeting for consideration and follow-up action. Note that the IRB has the authority to suspend or terminate the study in accordance with federal regulations and IRB policy until a written response is received from the Principal Investigator. Additionally, the IRB may exercise his/her authority to notify applicable institutional and outside agency officials of the principal investigator's failure to comply with NTR IRB policies and procedures.
 12. If there are not any documented findings during the compliance audit, a Post Approval Monitoring Checklist and memorandum will still be drafted and sent via Docu-Sign to the PI for his/her signature.
 13. If preliminary findings of non-compliance by the research compliance auditor or designee so indicate the safety and welfare of subjects is in jeopardy, the Executive Director of Research Compliance can immediately request the IRB Chairperson to suspend the protocol, including study enrollment and/or activities; and take appropriate action to ensure the safety and welfare of the subjects until this matter can be brought before the next IRB convened meeting for further review and determination. [See "When the safety and welfare of subjects are in jeopardy", below for further details].
 14. If the PI responds to the *Post Approval Monitoring Checklist / Memorandum* with his/her comments and/or acknowledgments, the research compliance auditor or his/her designee will compile the documents for IRB review and further recommendations, if needed. IRB review/acknowledgement of the *Final Audit Report* will be documented in the Meeting Notes/Chair's Report.

15. If no further follow-up is necessary, a copy of the *Board Action Notice* will be sent to the PI. If the IRB requests further follow-up, the PI will be notified of the IRB's determinations.

Failure to provide documents or access to records:

In order for effective and timely review of research protocols involving human subjects, during an compliance audits of such projects, the research compliance auditor or designee shall have full access to all documents and processes associated with the IRB-approved protocol. Failure to provide documents or access in a timely manner may result in immediate IRB suspension or termination of the approval status of the protocol. Additionally, applicable institutional officials sponsor(s), and/or regulatory agency officials shall also be notified of the status change of the protocol.

When the safety and welfare of subjects are in jeopardy:

In the event that a study is suspended, the IRB Chairperson will bring appropriate documentation to the next IRB convened meeting, and the Board will determine (by a simple majority vote) whether to rescind the suspension, uphold the suspension, or terminate approval of the study. The IRB will also decide the corrective and preventive action plan for the study, if any; and if applicable, the corrective and preventive actions plans for research personnel involved in the non-compliance. The corrective and preventive action plan agreed upon by the IRB will be documented and sent to the Principal Investigator.

Principal Investigator Involvement:

Additionally, a PI may be required to appear before the convened IRB or to meet with the IRB Chairperson to address issues and discrepancies identified during the compliance audit. If during the course of the compliance audit, subjects are considered at risk due to the actions of the PI or other key research personnel, appropriate officials of the institution in which the research is occurring (and, if applicable, the sponsor and regulatory agency of the research) shall be notified, and appropriate action will be taken, such as suspension and /or notifications, to ensure the safety and welfare of the subjects.

Follow-Up:

If significant findings are uncovered during a periodic compliance audit or a directed compliance audit, the research compliance auditor or designee may conduct a follow-up visit within six (6) months of the initial resolution of the compliance audit findings, or as otherwise instructed by the convened IRB.

Reporting:

A copy of the final compliance audit report and correspondence (s) will be maintained in the Office of Research Compliance.

Other UNTHSC personnel may be made aware of the audit findings as deemed appropriate by the Executive Director of Research Compliance and IRB Chairperson.

If required by federal regulations, applicable regulatory agencies will be notified.

Note, at all times the IRB Chairperson or designee may exercise his/her authority to notify applicable institutional officials and regulatory agencies of the principal investigator's failure to comply with NTR IRB policies and procedures.

List of Appendices

- A. UNTHSC IRB Federalwide Assurance (FWA) and DHHS Registration
- B. IRB Reviewer Checklists/Guidelines
- C. IRB Forms and Instructions
- D. Investigator Guidance
- E. Human Subject Regulations Decision Charts
- F. OPHS Correspondence
- G. List of UNTHSC IRB Members
- H. Core Regulatory/Ethical Guidance
http://ori.dhhs.gov/policies/fed_research_misconduct.shtml
- I. Post Approval Audit Checklist