The University of North Texas Health Science Center at Fort Worth

Institutional Review Board

Policies and Procedures Document

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SECTION 1: INTRODUCTION

SECTION 1.1 PURPOSE AND SCOPE OF THESE POLICIES AND PROCEDURES

All research projects with human participants conducted by faculty, staff, and students associated with The University of North Texas Health Science Center at Fort Worth (hereinafter referred to as UNTHSC) must receive ethical approval before the research is begun. The information in this Policies and Procedures document is designed to assist investigators with the process of achieving this approval. For more information about the Common Federal Policy for the Protection of Human Subjects, read 45 CFR, Part 46. For more information about basic ethical questions in the conduct of research, read The Belmont Report. These documents may be found on our web site at http://research.hsc.unt.edu/irb.html.

A brief review of these documents is provided here so that investigators may better understand the reasons for ethical review of research with human participants; the primary ethical principles that govern such research; and the statutory basis or enactment of these principles. This document also contains information that should be sufficient to allow researchers to submit an acceptable application for the review of a project involving human subjects. Investigators who read this document will be informed about the National Institute of Health (NIH) rules and UNTHSC requirement of education for all individuals responsible for the design and conduct of research projects with human subjects. Investigators will also be informed about their obligation to obtain an authorization from research participants for the disclosure of protected health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); in what circumstances the authorization may be waived; and the process involved in creating de-identified information in compliance with the HIPAA privacy rule.

SECTION 1.2 BACKGROUND INFORMATION

SECTION 1.2.1 ETHICAL VIOLATIONS IN RESEARCH WITH HUMAN PARTICIPANTS

Human researchers have treated other humans inhumanely and unethically. The Nuremberg trials documented the unethical behavior of Nazi physicians. American researchers from the Public Health Service studied 400 African American men with syphilis in the Tuskegee syphilis study between 1933 and 1972. These men were not asked for their informed consent/authorization to be in the study and they were, in fact, given misinformation about their treatment. After penicillin became available and was known to be effective in the treatment of syphilis, it was withheld from these subjects because the researchers were interested in the natural history of the disease. Researchers from Harvard and MIT formed a "science club" of 19 mentally impaired boys at the Fernald State School between 1946 and 1956. These boys were fed forms of radioactive iron or calcium, sometimes in their milk, to enable the researchers to study the body's ability to digest minerals. Doctors at the Jewish Chronic Disease Hospital conducted studies of human transplant rejection using cancer cells. The subjects were not asked for informed consent/authorization and did not give written consent/authorization to participate in the study. Between 1963 and 1966, children at the Willowbrook State School, a state school for "mentally defective" youths were purposely infected with the hepatitis virus in a study of that disease. During the course of this study the institution closed its doors to new clients, claiming overcrowding. However, the wing housing the hepatitis program was willing to admit new clients if their parents agreed to allow their children to participate in the ongoing studies. (These

descriptions of unethical research conduct are based on the NIH tutorial for ethical training. That training module is at http://ohsr.od.nih.gov/cbt/)

Behavioral and social science researchers have exposed other humans to severe trauma and psychological stress in the name of scientific research. The participants in Milgram's "obedience" studies, conducted in the early 1960s, were told that they had to continue to participate in the study and shock another person at increasingly intense voltages. Studies supported by the Human Resources Research Office of the U.S. Army introduced severe stress to army recruits by threatening them with death from errant artillery rounds or by causing the recruits to think that they, by making a mistake in wiring an instrument, had caused the injury or death of others in their units.

SECTION 1.2.2 CODES OF RESEARCH ETHICS

Codes of research ethics have been developed, in part to address the disregard for human safety and dignity that these research projects reflect. The Nuremberg Code of 1947 was the first international code of research ethics. Its first principle is "The voluntary consent/authorization of the human subject is absolutely essential." The accompanying text made it clear that this voluntary consent/authorization should also be informed consent/authorization: "...the person involved ... should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision." This principle of "free and informed consent/authorization" remains the basic foundation of ethical research with human participants.

Another early code was the Helsinki Declaration, adopted by the World Medical Assembly at its meeting in Helsinki, Finland in 1964. Its second principle, "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor..." established the concept of ethical review.

The first ethical code covering social and behavioral research was a set of 10 ethical principles adopted by the American Psychological Association in 1972, which has been updated effective June, 2003. The bases for these principles were critical incidents. Psychologists were asked to submit examples of research that they deemed unethical or of questionable ethics. The committee charged with developing ethical standards for psychological research then developed principles that would guide the conduct of researchers when conducting research that could pose ethical problems. The American Psychological Association's principles were the first to recognize the principle of confidentiality. Principle 10 states: "Information obtained about the research participants during the course of an investigation is confidential. When the possibility exists that others may obtain access to such information, ethical research practice requires that this possibility, together with the plans for protecting confidentiality, be explained to the participants as a part of the procedure for obtaining informed consent/authorization." Most professional organizations have ethical codes, and most require authors of manuscripts submitted to the journals of these organizations to state that they have followed these ethical principles in their research.

The U. S. Department of Health, Education, and Welfare issued ethical guidelines in 1971, which were codified into Federal Regulations in 1974. However, the primary impetus for current government ethical regulation began with the establishment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research under the aegis of the Department of Health, Education, and Welfare in 1974. The Commission was charged with identifying the basic ethical principles that should underlie research with human subjects. The report of the Commission, called The Belmont Report because it was based on deliberations held at the Smithsonian Institution's Belmont Conference Center, was published in 1978. The Belmont Report identified three basic ethical principles. They are:

(1) Respect for Persons (autonomy): This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent/authorization from all potential research subjects (or their legally

authorized representatives).

(2) Beneficence: This principle requires that researchers maximize benefits and minimize harms or risks associated with research. Research-related risks must be reasonable in light of expected benefits.

(3) Justice: This principle requires the equitable selection and recruitment and fair treatment of research subjects.

These three principles were the underpinnings of both an early (1980) version of a Common Federal Policy for the Protection of Human Research Subjects and the current version of that policy. The current version has been adopted by sixteen federal departments and agencies, including the Department of Health and Human Services, the National Science Foundation, the Department of Education, and the Central Intelligence Agency. The Food and Drug Administration (FDA) has concurred with the Federal Policy and has made changes in its IRB and informed consent/authorization regulations so that they correspond to the Federal Policy. This Federal Policy, sometimes called the Common Rule, is codified as the Common Federal Policy for the Protection of Human Subjects and was published in the Federal Register in 1991. It is referred to as 45 CFR 46 and its regulations underlie the decisions of IRBs. The regulations further require that each institution at which federally funded research is conducted adhere to the principles of The Belmont Report and set forth in writing its ethical principles, policies, and procedures. This institution's agreement to abide by the Belmont Report and by 45 CFR 46 (called a Federal Wide Assurance or FWA) is approved by the federal agency that oversees ethical issues in human research. Because UNTHSC has an FWA, UNTHSC can establish an IRB that can review all research projects involving human subjects.

SECTION 1.2.3 ADMINISTRATION OF RESEARCH ETHICS - FEDERAL

The audits conducted by the federal department responsible for human subject protection, now known as the Office for Human Research Protections (OHRP), of the performance of IRBs and the conduct of research with human participants at several medical schools have resulted in temporary injunctions of research with humans at those schools. The death of a participant in a gene therapy research study suggested a lapse of oversight at the site of that study. News reports of clinical trials have suggested that doctors may receive financial benefits by enrolling their patients in such trials and that the patients may not benefit or may be at risk.

SECTION 1.2.4 ADMINISTRATION OF RESEARCH ETHICS - THE UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER AT FORT WORTH

The Office of the Executive Vice President Academic Affairs of Research is responsible for the administration of research ethics at UNTHSC. That office oversees the functioning of the Institutional Review Board (IRB), the University committee that reviews proposals for research with human participants. The IRB itself works out of the Office of IRB Services.

If there are questions about the rules or procedures for ethical review or the applicability of the information in this manual to a proposal, first contact the Departmental Chair. Chairs serve as the liaison between the IRB and the faculty, staff, and students in the departments and colleges where research is conducted with human participants. If the Chair cannot answer the questions, contact:

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SECTION 1.3 REVISION AND MAINTENANCE OF THE POLICIES AND PROCEDURES

All new or revised materials will be placed on the IRB web page by the Office of Research.
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SECTION 2: DEFINITIONS

The following definitions are applicable to all sections of this document.

"Conflict of Interest:"
Growing interaction between for-profit enterprises and UNTHSC has created new possibilities for the occurrence of conflicts of interest. These conflicts arise when there are opportunities for faculty or staff members to benefit financially either from the outcome of research or from activities conducted in the course of responsibilities as an institutional research member.

UNTHSC believes that with clear guidelines and principles, in conjunction with appropriate supervision and monitoring, it is possible for interaction between industry and academic medicine to take place in a manner that is consistent with the highest traditions of medical and scientific research and in a way that energizes scientific creativity.

This Policy establishes guidelines for the appropriate structuring of relationships with industry and other outside ventures so as not to conflict with previously established responsibilities to UNTHSC. Investigators are expected to make reasonable inquiry as to whether their relationships and activities fall within the provisions of this Policy. It is not the intent of this Policy to eliminate or prohibit all situations involving a potential Conflict of Interest. This Policy is intended to enable Investigators to recognize situations that may pose a conflict of interest, to report these situations to the Conflict of Interest Committee, and to ensure that the Conflict of Interest Committee reviews these situations and, if necessary, supervises or monitors them. An integral part of this Policy is a disclosure mechanism whereby Investigators regularly review their activities. This Policy is intended to maintain the professional autonomy of scientists and physicians inherent in the self-regulation of science. This Policy should be viewed as complementing all institutional policies and procedures, including Sections 5.05 and 5.06 of UNTHSC's Personnel and Procedures Manual.

Each Investigator shall disclose all **significant financial interests**:

i. of the Investigator including spouse and dependent children
ii. that would reasonably appear to be affected by the research, educational, or service activities funded, or proposed for vending, by an external sponsor
iii. in entities whose financial interests would reasonably appear to be affected

by such activities.

What is covered?
Significant financial interests include:

a. Receipt of, or the right or expectation to receive monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees, honoraria, payments for directorships or executive roles); equity interests (e.g. stocks, stock options, dividends or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights); or
b. receipt of, or the right or expectation to receive other value, such as in the form of a forbearance, forgiveness, interest in real or personal property, rent, capital gain, real or personal property, or any other form of compensation, such as gifts.

The term **does not include**: interests held directly through funds such as mutual funds, pension funds, or other institutional investment fund in which the Investigator or the Investigator's Family does not control the selection of investments.

Further, the following financial interests do not rise to the level of a Significant Financial Interest:

1. salary, royalties, or other remuneration received from UNTHSC;
2. standard royalties received for published scholarly work or other professional writings;
3. royalties or equities received under UNTHSC royalty-sharing policies (see UNTHSC Intellectual Property Policy);
4. consulting fees received from an entity in which neither the Investigator, the Investigator's Family, an Associated Entity of the Investigator, nor UNTHSC have any other relationship, provided that the consulting relationship has been approved in accordance with the UNTHSC Outside Employment Policy, and subject to all other policy requirements including appropriate devotion of time to UNTHSC;
5. income from seminars, lectures, or teaching engagements sponsored by public entities; or
6. income from services on advisory committees or review panels for governmental entities.

"DHHS" means the Department of Health and Human Services.

"FDA" means the Food and Drug Administration.

"Federal Wide Assurance (FWA)" means a document that fulfills the requirements of 45 CFR Part 46 and is approved by the Secretary of Health and Human Services. The University of North Texas Health Science Center has an approved FWA on file with DHHS.

"HIPAA" is the Health Insurance and Portability and Accountability Act of 1996 (HIPAA) that protects the privacy of a research participant's health information. The three categories of IRB approval are maintained but the research protocol, and the activity conducted preparatory to the research, is required to meet additional

qualifications more fully explained below.

"Human Subject" means a living individual about whom the investigator conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable 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, and information, which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

"Informed Consent/authorization" means the knowing consent/authorization of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. Information conveyed in the informed consent/authorization procedure must include all essential elements listed in Section 4 of this manual.

"Institution" means any public or private institution or agency (including Federal, State and local Government agencies).

"Key Personnel" are defined as the principal investigators, co- investigators, and others specified within each project, as having decision-making power over the investigation.

- The principal investigator is that individual with signatory power on all documents related to the research project. This person has final authority over the project. The principal investigator accepts responsibility for training all personnel associated with the study in compliance with the human subject’s regulations of 45 CFR 46.

- The co-investigator is that individual who may be designated as a co-investigator in grant-related documents. The co-investigator reports to the principal investigator who is ultimately responsible for the conduct of the research.

- Others with decision-making power may include such persons as project managers, directors, trainers. These designations are not all-inclusive. Operationally, these individuals have some oversight responsibility for one or more portions of the project. Individuals in this category are determined uniquely for each project by the principal investigator.

"Legally authorized representative," means an individual or judicial or other body authorized under applicable law to consent/authorization on behalf of a prospective subject to that subject's participation in the particular activity or procedure.

"Minimal Risk" means that the risks of harm anticipated in the proposed research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Please note the different definition for minimal risk for incarcerated persons: 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.

"OHRP" means the Office for Human Research Protections. This is an office in the Office of the Secretary of Health and Human Services that is responsible for regulatory oversight of human subject research.

"Research" means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Research is defined by both the Common Rule of the Federal regulations and by the Privacy rule of HIPAA.

"Secretary" means the Secretary of Health and Human Services and/or any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

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SECTION 3: THE INSTITUTIONAL REVIEW BOARD

SECTION 3.1 DESIGNATION OF THE INSTITUTIONAL REVIEW BOARD

The University of North Texas Health Science Center at Fort Worth has one (1) Institutional Review Board (hereinafter referred to as the IRB) that is responsible for conducting initial and continuing reviews and providing oversight for all research activities involving the use of human subjects performed on the campus or at any location under the purview of UNTHSC. The IRB will conduct initial and continuing reviews of research activities according to the procedures outlined in this document. All review procedures will meet or exceed the requirements set forth in 45 CFR 46.

To ensure compliance with the regulations, the University of North Texas Health Science Center has adopted an internal audit and/or self-assessment procedures designed to assure proper protocol and consent document preparation, protocol submission, review and approval by the IRB, and timely monitoring of protocol implementation. One example is the use of approval date stamps on consent documents and protocols to ensure that the Federal requirement of at least annual IRB review of each protocol is met. A second example is the use of standardized language endorsed by the institution, which meets the regulatory requirements and which is customized and elaborated upon by the investigator in creating an appropriate informed consent document.

Specification of quality standards in the conduct of research is an important function of the institutional leadership. Insistence upon well-conceived and well-conducted research should be evident both in written policies and in actions of institutional officials. Research that is conducted so poorly as to be invalid exposes subjects and the institution to unnecessary risk.

SECTION 3.2 CHARGE TO THE INSTITUTIONAL REVIEW BOARD

The University of North Texas Health Science Center (UNTHSC) has established a standing committee, Institutional Review Board (IRB), of members with the experience and expertise charged with the review of research involving the participation of human subjects and the protection of their rights and welfare. The IRB is charged with the responsibility to review and approve, disapprove or require modifications in all research involving the participation of human subjects that is:

Sponsored by the UNTHSC;

Conducted by or under the direction of any employee or agent of UNTHSC in connection with his/her institutional responsibilities;

Conducted by or under the direction of any employees or agent of UNTHSC using institutional property or assets; or

Facilitated by the use of the institution's non-public information to identify or contact subjects or prospective subjects.

The IRB may also review other human subject research pursuant to formal affiliation agreements between UNTHSC and other organizations.

The IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of this institution.

The ethical framework for this charge consists of the ethical principles regarding all research involving humans as subjects, as set forth in the Nuremberg Code, the Declaration of Helsinki, and the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research [the "Belmont Report"], regardless of whether the research is subject to Federal regulation or with whom conducted or source of support (i.e., sponsorship).

The IRB operates under assurance of the Office for Human Research Protection (OHRP) and in accord with the regulations of the Food and Drug Administration (FDA) and in compliance with other State and federal regulations as applicable.

Federal Wide Assurance (FWA) covers the following entities:

Texas College of Osteopathic Medicine

Graduate School of Biomedical Sciences

School of Public Health

SECTION 3.3 FACULTY BYLAWS

The IRB is a standing committee established under the Faculty Bylaws of UNTHSC. Therefore, the bylaws as a whole provide the basis and framework under which the UNTHSC bylaws operate. The IRB is addressed in Article XVI, Section H – Institutional Review Board:

1. Composition: The board shall consist of a minimum of nine members of the faculty appointed by the President of UNTHSC to serve for three years. The Chair will be elected from among the members of the Board, subject to approval of the President. The Chair may request additional faculty members to be appointed by the President as needed by increased workload. The President will appoint certain community members as mandated by federal regulations in addition to the above cited faculty members. The Associate Vice President of Research will be an ex-officio member.

2. Responsibilities: The IRB is responsible for review and approval of all research involving human subjects. Research involving human subjects cannot be conducted without the approval of the IRB. Federal guidelines for the conduct of research involving human subjects are provided by the United States Department of Health and Human Services.

3. Minutes: Copies of the minutes of the IRB are available to all faculty members.

SECTION 3.4 COMPOSITION OF THE INSTITUTIONAL REVIEW BOARD

The President of UNTHSC will solicit names for appointments from a variety of sources, e.g., past and present IRB members, and UNTHSC staff. The names of persons in ethics and healthcare, who have demonstrated experience and/or interest regarding the protection of the rights and welfare of human volunteers in research, will be considered for possible contact and appointment. As IRB members rotate off and new members are appointed, selections will be made to assure continuing compliance with the requirements of 45 CFR 46.107 regarding gender and diversity.

The committee must be sufficiently qualified through the maturity, experience, and expertise of their members and diversity of membership to insure respect for their advice and counsel specific to safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the committee must be able to ascertain the acceptability of proposals in terms of organizational commitments, regulations, applicable law, standards of professional conduct and practice, and community attitudes.

In addition to faculty members representing different disciplines, the IRB currently has three non-affiliated members who are deemed to represent non-scientific areas. At times, the IRB may not have the necessary expertise to judge the scientific soundness of a research protocol and may be unable to make a fair and accurate determination of the risk-benefit ratio. For these protocols, the IRB may call upon ad hoc consultants for assistance in review for scientific merit.

Member files are kept in the IRB Services Office. They include 1) a letter of appointment, 2) a current curriculum vitae (as appropriate), and 3) documentation of a certificate that shows the member has completed the UNTHSC tutorial for IRB members and investigators.

Educational materials are generally distributed and discussed at each IRB meeting.

SECTION 3.5 CHAIRPERSON

It is the responsibility of the President to confirm the Chairperson. This appointment is made for a three-year period. In the absence of the Chair, the Vice Chair (an IRB member) has signatory authority.

SECTION 3.6 MEETINGS

The IRB shall hold one regularly scheduled meeting per month, at a time and place to be pre-determined (See Section 6 and 7 for specific details).

SECTION 3.7 CONFIDENTIALITY OF THE REVIEW PROCESS

During the process of initial or continuing review of an activity, material provided to the Institutional Review Board shall be considered privileged information and the Board shall assure the confidentiality of the data contained therein. All members of the IRB sign a Confidentiality Agreement.

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SECTION 4: EDUCATION

SECTION 4.1 MEMBER EDUCATION

On appointment to the IRB, each member is given his or her own copy of the UNTHSC IRB Reference Manual. This manual contains the following material:

- UNTHSC Multiple Project Assurance/Federal Wide Assurance
- UNTHSC IRB Membership Roster
- UNTHSC IRB Written Procedures
- The Belmont Report
- Nuremberg Code
- Declaration of Helsinki
- DHHS Regulations (45 CFR 46) and Miscellaneous OHRP Guidance
- FDA Regulations (21CFR 50 & 56) and Select Information Sheet
- UNTHSC Investigator's Reference Manual Including Sample Documents & Key Policies
- Research Ethics and Regulations, Education Resources

At most meetings pertinent articles regarding the participation of human subjects in research is distributed and discussed.

SECTION 4.2 REQUIRED EDUCATIONAL TRAINING

In accordance with federal regulations, it is necessary for all individuals identified as "key personnel" to complete required educational training on the protection of human research subjects. **Key personnel include all individuals responsible for the design and conduct of the study.**

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 has successfully completed the online educational tutorial located on the UNTHSC web site (http://research.hsc.unt.edu/dhhs/irb.html). No protocols will be reviewed for new or continuing review that are not in compliance with this requirement.

All IRB members have completed the required training.

SECTION 4.3 CHAIR AND STAFF EDUCATION

The Chair and staff members attend at least one national meeting each year that focuses on participation of human subjects in research. PRIM&R, ARENA, ACRP and specific workshops sponsored by OHRP are some of the resources of which they avail themselves.

SECTION 4.4 CONTINUING EDUCATION

In-services are given by the staff of the IRB Services Office as requested by Departments or Schools. The Office has scheduled three educational sessions for 2004 for general education for investigators and coordinators:

February 10 - Informed Consent
April 13 - HIPAA regulations
June 8 - Continuing Review of Research

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SECTION 5: GENERAL IRB POLICIES

SECTION 5.1 APPLICABILITY

The procedures set forth in this document are applicable to all faculty, staff, employees, and students at the University of North Texas Health Science Center who propose to use humans as subjects in research, development, and related activities.

SECTION 5.2 FUNCTIONS AND RESPONSIBILITIES

A. Safeguarding the rights and welfare of subjects at risk in any research activity, whether financially supported or not, and irrespective of the source of any supporting funds, is primarily the responsibility of the institution. In order to provide for the adequate discharge of the institutional responsibility, no research activity involving human subjects may be undertaken by any faculty, staff, employee or student at the University of North Texas Health Science Center unless our IRB has reviewed and approved the research prior to commencing the research activity.
B. The review will determine whether the subjects will be placed at risk and, if risk is involved, that:

1. Risks to subjects are minimized (This is an essential condition for approval);

2. The risks to the subject are so outweighed by the sum of the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

3. The rights and welfare of any such subjects will be adequately protected;

4. Legally effective informed consent/authorization will be obtained by adequate and appropriate methods in accordance with the provisions of Section 4 of this manual; and

5. The conduct of the activity will be reviewed at intervals determined by the IRB, but not less than annually.

C. The determination of when an individual is at risk is a matter of the application of common sense and sound professional judgment as it relates to the circumstances of the research activity in question.

1. The IRB will carefully weigh the relative risks and benefits of the research procedures to be applied to the subject.

2. Research activities designed to yield fruitful results for the benefit of individual subjects or society in general may incur risks to the subjects provided such risks are outweighed by the benefit to be derived from activities.

3. The degree of risk involved in any activity should never exceed the humanitarian importance of the problems to be solved by that activity. Likewise, compensation to volunteers should never be such as to constitute an undue inducement to the subject.

4. There is a wide range of medical, social and behavioral research projects and activities in which no immediate physical risk to the subject is involved; e.g., those utilizing personality inventories,

interviews, questionnaires, or the use of observation, photographs, taped records, or stored data. However, some of these procedures may involve varying degrees of discomfort, harassment, or invasion of privacy.

5. There may also be projects that involve tissues, body fluids, and other materials obtained from human subjects. The use of these materials obviously involves no element of physical risk to the subject. However, their use for research, training, and service purposes may present psychological, sociological, or legal risks to the subjects. In these instances, application of the policy requires IRB review to determine that the circumstances under which the materials are to be procured are appropriate and, if the subject is deemed to be at risk, that adequate and appropriate consent will or can be obtained for the use of these materials for research purposes.

6. Similarly, some studies depend upon stored data or information that was often obtained for quite different purposes. Here, the IRB will determine whether the use of these materials is within the scope of the original consent/authorization, or whether consent/authorization should be obtained or waived.

D. If the proposed activity involves an investigational drug, biological material, or device, it is the policy of the University of North Texas Health Science Center IRB that before these test articles may be tested on humans at this institution, or before an FDA-approved drug can be used for unapproved indications, the sponsor must obtain a Food and Drug Administration exemption [Investigational new Drug (IND) or Investigational Device Exemption (IDE)] before the activity will be approved by the IRB.

E. The Institutional Review Board shall not approve any activity involving human subjects unless the principal investigator is a faculty member, staff or student of The University of North Texas Health Science Center or unless a faculty member at the above institution agrees in writing to assume responsibility for the subjects involved.

F. Any activity involving the use of radioactive materials must have approval by the Radiation Safety Committee before it can receive final approval by the IRB.

G. Compliance with this policy or the procedures set forth herein will in no way render inapplicable pertinent laws of the State of Texas, any local law which may bear upon the proposed activity or the Rules and Regulations of the Board of Regents of the University of North Texas Health Science Center.

SECTION 5.3 TYPES OF PROTOCOL REVIEW

Three types of review may be conducted by the Institutional Review Board to ensure that all research involving human subjects conforms to Federal Regulations: (1) Ascertain that research meets the criteria for exemption from full board review; (2) Ascertain that research meets the criteria for expedited review; and (3) full Board review of research at a convened meeting.

SECTION 5.4 PROCEDURE TO BE FOLLOWED BY THE IRB FOR DETERMINING WHICH PROJECTS NEED VERIFICATION FROM SOURCES OTHER THAN THE INVESTIGATORS

A. To determine that no material changes have occurred in a project since previous IRB review, the IRB will utilize some or all of the following criteria;

1. Review of randomly selected projects;

2. Review of complex projects involving unusual levels or types of risk to subjects;

3. Review of projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB;

4. Review of projects where concerns about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources.

B. If it is determined that material changes have occurred in a project without IRB notification, review or approval, the IRB will meet and take appropriate action depending on the seriousness of the noncompliance.

C. Any action taken by the IRB shall be reported to the Executive Vice President Academic Affairs of Research or designee, the Department Chair, the appropriate Dean, and if indicated, the President of UNTHSC. All material noncompliance will be reported to the cognizant federal agency.

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Section 6: Initial IRB Review of Activities Proposing to Use Human Subjects in Research

SECTION 6.1 GOVERNING PRINCIPLES

The governing regulations for UNTHSC's IRB are 45 CFR Part 46 and 21 CFR Parts 50, 56, 312, and 812, and by HIPAA. The UNTHSC's Federal Wide Assurance with OHRP specifies that the institution will follow 45 CFR 46 for all funded and non-funded research.

SECTION 6.2 REQUIREMENTS FOR INITIAL IRB REVIEW

Any faculty member, staff or student from UNTHSC who proposes to engage in any research activity involving the use of human subjects must submit the following to the IRB Office:

1. a completed original IRB Application Form with Principal Investigator and Departmental Chair's signature;

2. a protocol describing the rationale for the study, research questions to be answered, methods, procedures, data analysis plan, and other pertinent information.

3. four complete copies of the DHHS grant application, if applicable, and

4. an informed consent form in UNTHSC's IRB approved format or justification for Waiver of Informed Consent or Waiver of Documentation of Consent;

5. if the study involves the use of questionnaires, surveys or similar instruments, copies of same must be submitted; and

6. In accordance with federal regulations, it is necessary for all individuals identified as "key personnel" to complete required educational training on the protection of human research subjects. **Key personnel include all individuals responsible for the design and conduct of the study.**

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 has successfully completed the online educational tutorial located on the UNTHSC web site (http://research.hsc.unt.edu/dhhs/irb.html). No protocols will be reviewed for new or continuing review that are not in compliance with this requirement.

* A "human subject" is defined as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information (45 CFR 46.102(f)).

SECTION 6.3 SUBMISSION SCHEDULE REQUIREMENTS

Presently, there is one IRB meeting per month. Meetings are held on the first Tuesday of each month. The meeting/submission schedule is distributed to every department and all investigators who conduct research before the beginning of the new fiscal year (September 1st). Protocols must be submitted to the IRB office by 5 p.m. of the deadline date listed. The submission packets must have all individual forms stapled and

collated. The deadline for submission packets is approximately two (2) weeks prior to the meeting date. An attempt is made to send the packets to the IRB members at least two weeks prior to the meeting date.

If the study is eligible for an "Expedited or Exempt Review" process, two copies of the list of materials described above should be submitted. Such protocols may be submitted at any time and will receive appropriate review and approval (See "IRB Review Process - Minimal Risk Protocols" below and for examples of research qualifying for "Expedited Review").

SECTION 6.4 REVIEW FOR EXEMPT STATUS

If requested by the Principal Investigator, the Chair of the IRB will determine whether a research proposal is exempt from review by the full Board. If a researcher believes their research meets the exempt criteria, they should submit two copies of the Statement by Principal Investigator (IRB Form 1) with a cover memo detailing the reason for the exemption (citing exemption number). Only the involvement of human subjects in one or more of the cited categories warrants an exemption.

SECTION 6.4.1 EXEMPT STATUS CRITERIA (as cited in 45 CFR 46.101)

The following are the categories that qualify for exempt status:

#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:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

#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 criteria #2 of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) 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 if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The Principal Investigator will normally be notified within one week if the project meets the criteria for exempt status. **It should be noted that the IRB has the authority to decline a request for exempt status based upon factors such as age of subjects (children), health of subjects, etc.**

SECTION 6.5 EXPEDITED REVIEW

A research investigator may request that their proposal receive an expedited review by the board. An expedited review will consist of review by the Chair or by one or more members of the IRB designated by the Chair. If an expedited review is requested, two copies of the Statement by Principal Investigator (IRB Form 1), along with a cover memo detailing the justification for the expedited review (please cite the expedited review research category number), should be submitted. Investigators should allow two weeks for notification of expedited review results. **It should be noted that the IRB has the authority to decline a request for expedited review, and require a full board review, based upon factors such as age of subjects (children), health of subjects, etc.**

SECTION 6.5.1 APPLICABILITY:

A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the applicable research categories, may be reviewed by the IRB through the expedited review procedure. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

B. The categories in this list apply regardless of the age of subjects, except as noted.

C. The expedited review procedure 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 subject's 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.

D. The expedited review procedure may not be used for classified research involving human subjects.

<u>Research Categories</u>:

#1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. NOTE: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

#2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

a. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which

it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

#3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:

a. Hair and nail clippings in a nondisfiguring manner;

b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

c. Permanent teeth if routine patient care indicate a need for extraction;

d. Excreta and external secretions (including sweat);

e. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

f. Placenta removed at delivery;

g. Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

j. sputum collected after saline mist nebulization.

#4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing (studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications). Examples of permissible procedures 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 height 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 be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.

#6. Collection of data from voice, video, digital, or image recordings made for research purposes.

#7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. This listing refers only to research that is not exempt.

SECTION 6.6 FULL BOARD REVIEW

SECTION 6.6.1 INTRODUCTION

The Institutional Review Board (IRB) is responsible for protecting the welfare and rights of individuals who are subjects of any research, whether funded or unfunded, whether on or off campus, which is conducted by faculty, staff or students. If the proposed research does not satisfy the guidelines for exempt or expedited review, the IRB as a full committee will consider the proposal.

SECTION 6.6.2 PROCEDURES

By 5:00 p.m. on the 3rd Monday of the month, the Principal Investigator will submit the original and 16 copies of IRB Form 1 to the IRB Office. If the project is a clinical trial, two complete copies of the pharmaceutical company protocol and the Investigator's Brochure must be submitted for review. All other projects must be accompanied by two complete copies of the grant application (the title of the IRB submission must match the title of the grant application).

The administrative staff will collate the following information on each new full board review project for inclusion in the packets to be distributed to each IRB member approximately two weeks prior to the next convened meeting:

IRB Form 1 (Use of Human Subjects Statement by Principal Investigator)
NOTE: IRB Form 1 includes all elements of the protocol description, informed consent and any advertisements

The IRB Chair and Vice Chair, in addition to receiving each of the items listed above, will also receive:

Copy of the drug company protocol or grant application
Copy of the Investigator's Brochure

NOTE: Upon receipt of their packets, members of the IRB are encouraged to contact the administrative staff for copies of any additional materials they will require to conduct their review.

When it is determined that consultants or experts will be required to advise the IRB in its review of a protocol, the research protocol will be distributed to the consultants or experts approximately two weeks prior to the next scheduled meeting.

SECTION 6.6.3 REVIEW

IRB review of research must be substantive and meaningful. Each project will be presented and discussed individually. Each project will be voted upon individually.

A majority of the membership of the IRB constitutes a quorum and is required in order to convene a meeting for the review of protocols. An IRB member whose concerns are primarily in non-scientific areas must be present at the convened meeting before the IRB can conduct its review. An IRB member who is not affiliated with UNTHSC must be present at the convened meeting before the IRB can conduct its review.

For a research protocol to be approved, it must receive the approval of a majority of those members present at the convened meeting. No IRB member may participate in the review of any project in which they have a conflicting interest, except to provide information requested by the IRB. That IRB member must leave the room during discussion and when the vote is taken.

The IRB will consider the following during their discussion of each new project:

- Scientific Design in Relation to Subject Safety
- Risks/Benefits
- Subject Selection (populations to be studied and recruitment plan)
- Additional Safeguards for Vulnerable Subjects
- Minimization of Risks to Subjects
- Privacy and Confidentiality
- Informed Consent (assuring that all required elements are present)
- Additional Considerations (e.g. collaborative research, international research, device study)

It is the responsibility of the IRB to determine whether or not vulnerable populations (e.g. children, pregnant women) may participate in the research.

The board must assign a level of risk. There are times when the risks associated with a particular project are such that continuing review should take place more frequently than annually. In these cases, the IRB will specify that the Principal Investigator reports to the IRB at a more frequent interval (e.g. 6 months).

The board will make one of the following recommendations regarding the disposition of the new project:

Protocol is approved as submitted
Protocol is approved contingent upon specific conditions (stipulations and/or recommendations)
Protocol is tabled pending substantial changes and resubmission
Protocol is disapproved

If the protocol is approved contingent upon specific conditions (stipulations and/or recommendations), the board must designate whether those stipulations and/or recommendations are to be reviewed by the IRB Chair, by a subcommittee of the IRB, or by the full IRB.

SECTION 6.6.4 PRINCIPAL INVESTIGATOR NOTIFICATION

After the convened IRB meeting, the disposition of the project is relayed to the Principal Investigator by IRB Form 2 (Board Action Form), normally within 3 working days. Any stipulations and/or recommendations will also be relayed.

Approval is granted for a period of not more than one year. Depending upon the degree of risk to subjects, approval may be given for less than one year. In addition, as a condition of approval, the IRB provides for the continuing review of all projects **at least** annually.

SECTION 6.7 MODIFICATION OF DECISIONS MADE BY THE INSTITUTIONAL REVIEW BOARD

Approvals, favorable actions, and recommendations made by the IRB are subject to review and further restriction by the institutional administration (HSC Deans, Executive Vice President Academic Affairs of Research , President). For example, protocols could be approved by the IRB on a scientific and ethical basis, but be restricted or disapproved by institutional administration due to the potential for adverse public/community reaction. Protocol disapproval, restrictions or conditions imposed by the IRB upon any activity involving human subjects cannot be rescinded or removed except by subsequent action of the IRB.

SECTION 6.8 NON-ADHERENCE TO INSTITUTIONAL REVIEW BOARD DECISIONS

Any reported significant deviation in activities previously approved by the IRB would be the subject of further inquiry by the IRB. In the event that the IRB finds reasonable evidence that restrictions, stipulations or decisions of the IRB have not been adhered to, the Chairperson shall brief the IRB, at the next scheduled convened meeting or at a specially convened meeting, on the details of non-compliance. The IRB will then determine what restrictions, conditions, or other actions are necessary to resolve the non-compliance and what procedures will be required to prevent future occurrences. The PI will then be notified in writing of the requirements necessary to assure compliance with the restrictions and decisions of the IRB. All instances of non-compliance will be reported to the Executive Vice President Academic Affairs of Research or designee. If serious or ongoing, instances of noncompliance must be reported to the regulating agency (OHRP, FDA, or both).

The Executive Vice President Academic Affairs of Research or designee will apprise appropriate members of the Administration, on a need to know basis. The Confidentiality of both research subjects and investigator will be protected as far as possible under current local, state and federal law.

If further action is necessary, the institutional policies and procedures relating to Misconduct in Science will be implemented.

SECTION 6.9 IRB MINUTES

The minutes of the prior meeting are approved at the subsequent IRB meeting. Minutes include a list of all studies that were voted on at the subsequent meeting, as well as a list of all actions that were taken administratively during the previous month. Minutes include separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB. The vote on all IRB actions include the number of persons voting for, against, and abstaining, in order to document the continued existence of a quorum. The minutes include the documentation of risk, as well as any potential conflict of interest that an IRB member may have with a particular protocol.

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SECTION 7: MEDICAL DEVICE STUDIES

The Investigational Device Exemption (IDE) regulations (21 CFR part 812) describe two types of device studies, “significant risk” (SR) and “nonsignificant risk” (NSR).

SECTION 7.1 SIGNIFICANT RISK DEVICE

A SR device study is defined (21 CFR 812.3(m)) as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is an implant; or (2) is used in supporting or sustaining human life; or (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.

SECTION 7.2 NON-SIGNIFICANT RISK DEVICE

A NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of “minimal risk,” to identify a study that may be reviewed through the expedited review procedure.

SECTION 7.3 DETERMINATION AS TO CATEGORY OF RISK

The IRB, regardless of the classification (SR or NSR) of the device assessed by the sponsor, must make its own assessment of the classification based on the proposed use of the device in a study, and not on the device alone. This must be accomplished **prior** to submission for full board review. An investigator considering participation in a device study must provide the Chair of the IRB with the following information:

1. Reports of prior investigations conducted with the device.

2. The proposed investigational plan.

3. A description of subject selection criteria.

4. Monitoring procedures.
   Information from the sponsor regarding risk assessment and the rationale used in making its risk determination.

5. If the device is already FDA approved, information on whether or not this is an “off-label” use of the device.

The IRB Chair may agree or disagree with the sponsor’s initial assessment. If the Chair agrees with the sponsor’s initial NSR assessment, the investigator will be notified in writing that the study may then be submitted for full board review (for confirmation of NSR classification and review of the study). If the Chair assesses the device as SR, the investigator and the sponsor will be notified in writing of the SR decision. The sponsor must notify the FDA that a SR determination has been made. The study can be submitted for full board review only after the sponsor has received FDA approval of an IDE application. If this is an investigational or “off-label” use of the device, the investigator must also comply with federal requirements for submission of an IDE, unless all of the conditions in 21 CFR 312.2(b)(1) are met.

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SECTION 8: USE OF DRUGS IN INVESTIGATIONAL ACTIVTIES

SECTION 8.1 APPLICABILITY

This policy applies to ALL use of a drug in an investigational setting, whether FDA-approved or not, and whether used for clinical or research purposes.

The FDA (21 CFR 312.3) defines a clinical investigation as "any experiment in which a drug is administered to, or used involving, one or more human subjects." Based on this definition, there are no exceptions to the requirement that any drug used in research with humans must be reviewed by the IRB and, in addition, is subject to FDA regulation.

This includes both Drugs and Biologic products.

SECTION 8.2 IND (INVESTIGATING NEW DRUG) APPLICATION

All drug use in research must include submission of an IND. The **ONLY** exception is if the marketed drug or biologic product meets **ALL six** of the following conditions:

i. It 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 the labeling for the drug;
ii. It is not intended to support a significant change in the advertising for the product;
iii. It 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 drug product;
iv. It is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
v. It is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7); and
vi. It does not intend to invoke 21 CFR 50.24 (this has to do with waiver of informed consent in an emergency room setting).

If your study does not meet **ALL** six of these conditions, or is an unapproved drug or unapproved use of a new drug, you must submit and IND, or provide written evidence from the FDA that an IND is not required. Because of the potential risk involved, the IRB will require an IND submission if there is any doubt that your study meets these six criteria.

Refer to the FDA website for instructions.

Currently, we have two contact numbers available.

A Food and Drug Administration
Division of Drug Information, HFD-240
5600 Fishers Lane, Rockville, MD 20857
Fax number: 301-827-4577
Email: druginfor@cder.fda.gov
Contact at the FDA: Barry Poole at 301-827-4570

Send:

- Your name, address, phone number, fax number, Email address, and affiliation.
- The name and a brief description of the substance to be administered, the source (e.g., animal, synthetic, etc.), dosage form, sterility (if applicable) and supplier

- A brief summary of the study including the purpose, hypothesis, number of subjects, patient population, condition or disease (if applicable), dose, route, and duration of substance administration.
- A brief explanation of why you consider the substance safe for administration to human subjects under the conditions of the study (append references, if necessary).

B. The FDA has also established a Pre-IND consultation Program that you may contact for guidance and instructions:

U.S. Food and Drug Administration
Office of Drug Evaluation IV (HFD-104)
Pare-IND Consultation Program
ATN: Sylvia D. Lynche, PharmD
9201 Corporate Blvd, 4th Floor
Rockville, MD 20850
Phone: 301-827-2335

SECTION 8.3 RESEARCH INVOLVING AN FDA-APPROVED USE

If the proposed use of a drug in a study is fully within the guidelines for use approved by the FDA, and meets the six criteria listed in Section 8.2, then an IND is not required.

However, the protocol submission should contain a summary of known risks and precautions associated with the drug, including any new data that has emerged the drug or biologic received FDA approval.

SECTION 8.4 RESEARCH INVOLVING AN OFF-LABEL USE OF AN APPROVED DRUG.

An off-label use of a drug in experimental setting will generally require submission of an IND. Again, refer to section 8.2. **THIS IS TRUE EVEN IF THE DRUG IS COMMONLY USED IN A CLINICAL SETTING FOR THE "OFF LABEL" CONDITION OR DOSAGE**.

Purely clinical, non-research use of a drug in an off-label manner is outside the jurisdiction of the IRB and is covered by other regulations of the UNTHSC and the physician's license.

SECTION 8.5 RESEARCH INVOLVING A NEW OR UNAPPROVED DRUG

Any investigation involving the use of a new drug, or any drug that does not have formal FDA approval, will require an IND. **NO EXCEPTION** will be made without written documentation from the FDA.

SECTION 8.6 SUBMISSION AND REVIEW PROCEDURES

IN ADDITION to the requirements of the IRB contained in other policies and procedures, the following procedures apply.

A. For **ON-LABEL**, approved use:

Submit the study protocol as usual, but include:

1. Information supporting your use as an approved use
2. Updated safety and efficacy information. You are responsible for conducting a current literature review as outlined in section 8.6.

B. For **ALL** other uses, the submission should include:

1. The IND number and name of the sponsor (if different than the investigator)
2. The generic, chemical, and trade name of the drug and its structural formula.
3. An abstract of the available information concerning the animal pharmacology and toxicology.
4. A summary of previous clinical studies. This should include any adverse effects or toxicity. Pertinent references should be included. See Section 8.6 for guidelines.
5. A specific indication of the Phase (i.e., I, II, III, or post-marketing surveillance) should be included.

C. The UNTHSC-IRB will review the project in two parts.

1. Upon submission for full-board review, the chair will assign the protocol to a member of the board who has specific training in pharmacology; of an appropriate member is not available, it will be assigned to an outside consultant.

2. The reviewer will conduct a Pharmacy and Therapeutics (P&T) review to evaluate the protocol and drug for safety for the proposed use, and make one of three recommendations: approval, modification, or disapproval. If the reviewer recommends modifications or disapproval, the investigator must satisfy the recommendations of the reviewer. **NO STUDY** will be approved until cleared for approval by the pharmacy and therapeutics reviewer.

3. The IRB will then conduct a full board review.

D. Since the UNTHSC does not have a separate pharmacy and therapeutics committee, there is no time estimate for this review process. Since the study cannot go forward until cleared, the investigator is strongly advised to submit the study as early as possible.

SECTION 8.7 DOCUMENTATION GUIDELINES

The following guidelines are adapted from those in place at Johns Hopkins University.

When a study involving a drug or biologic is submitted for review, the IRB must have access to sufficient information to determine if the drug is sufficiently safe to use in the subjects of the study. The standard the investigator must reach has been raised in recent years due to situations where negligent documentation by investigators and negligent review by IRBs have resulted in the death of otherwise healthy research subjects. The investigator should strive to provide more than the minimum data and be prepared for careful scrutiny of any use of drugs or biologics with humans.

This means the investigator must conduct and provide evidence of a thorough review of the literature for safety of the proposed agent. What this means in practice will vary widely. For example, sponsored drug trials are usually presented to the local investigator with extensive, current documentation, so that the local investigator's obligation will be to be familiar with the data, be prepared to report to the IRB (and sponsor) any additional safety data, and transmit the materials to the IRB for review. This is normally also a requirement by the sponsor. A study involving an established, approved use of an approved drug will also require a simple updated literature review to supplement that available from the drug manufacturer. At the other extreme, an agent that has not been approved by the FDA for any use will require an extensive and comprehensive review of the literature. If the study is investigator-initiated, then the **ENTIRE** responsibility for that documentation falls to the investigator.

The standards given here apply to the latter case, that is, where the study is of an off-label or unapproved use or use of an unapproved drug. However, the IRB and the P&T reviewer have the responsibility of

assessing whether the submitted documentation is adequate and have the obligation to request additional documentation if, in their judgment, the provided documentation is inadequate or incomplete. The IRB members and the P&T reviewer also have the option to conduct an independent literature review.

The investigator should conduct a thorough and complete review of the literature. It is **NOT SUFFICIENT** to simply order a computerized search. The search may include reviews, textbooks, abstracts, meeting notes, meeting synopses, and advertisements but are not sufficient. It should also include primary peer reviewed publications.

The investigator should also remember that a substantial amount of information may be unpublished, and other information may predate the years covered by an automated search. The investigator is responsible for showing that an active effort was made to search out those sources. For example, a published paper may not contain all the data from a study, and direct contact with the study authors might reveal information affecting subject safety. Investigators have been cited when auditors believed that the investigator knew or should have known about such unpublished data.

The investigator should provide three sets of information:

A. A summary of the literature review, detailing the findings regarding the safety and toxicity of the agent, including data from both human and animal studies.

B. A Literature Search Log showing the information sources used as well as the search paths that have led to that information. The search log should include information showing:

1. Date search conducted
2. Name of database
3. Host
4. Latest update available
5. Years searched
6. Print-out of your search strategy (not a retyped form, but rather the original strategy)

C. Bibliography

Johns Hopkins recommends the following search strategy be used as a general guideline:

1. Identify the drug
2. Check for alternate names of the drug
3. Define the research setting in which the drug will be used
4. Consult reference or tertiary sources as a starting point
5. Consult secondary sources (abstracting and indexing services) for comprehensiveness and quality assurance.
6. Choose the most appropriate sources of evidence of safety/adverse effects
7. Create a bibliography

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Section 9: Informed Consent

SECTION 9.1 GENERAL REQUIREMENTS

Principal investigators are responsible for obtaining written informed consent in accordance with federal regulations and for ensuring human subjects will not be involved in research prior to obtaining consent.

Each of the following points MUST be included in the consent document, except where the point is irrelevant to the research.

SECTION 9.2 ELEMENTS OF INFORMED CONSENT/ASSENT FORMS

1. A statement that the study involves research, an explanation of the purpose of the research and why the subject is asked to participate.

2. A description of the procedures and identification of any procedures which are experimental. For example, the description of procedures should include the length and frequency of hospitalizations; number, length and frequency of clinic visits; total amount of time a subject should expect to devote to the study; names and types of medication; types and number of tests; amount of blood to be drawn noted in tablespoons or teaspoons; use of questionnaires; special diets; withholding of standard treatment; follow-up studies; and randomization, use of placebo, double-blind, or cross-over methods. In the case of patient subjects, state clearly which procedures are experimental and which procedures would be performed for medical reasons if the patient were not a research subject.

3. A description of any reasonable risks or discomforts to the subject. These may include drug side effects, hazards of procedures, or withholding therapy of proven value. Describe what will be done to minimize the risks, counteract side effects, and which side effects might be irreversible.

4. A description of any benefits to the subject or to others which may reasonably be expected from the research.

5. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. It is not necessary to provide a full account of the risks and benefits of standard alternative treatments in the consent form.

6. A statement describing the extent to which confidentiality of records identifying the subject will be maintained. FDA and sponsor inspection of records in studies involving drugs and devices should be explained. The means of disclosure of information obtained during the study should be described, e.g., publication, entry in medical records, or transmission to another physician.

7. An explanation that only emergency medical treatment is available if a research-related injury occurs. If a company or agency sponsoring the research agrees to provide for additional treatment and/or monetary compensation for injuries and that agreement has been approved by the UNTHSC legal counsel, this should be included in the consent form.

8. A statement of additional costs to the subject for research procedures.

9. A statement of the amount of compensation for time and travel expenses associated with a subject’s participation in the study. The compensation must not be contingent upon completion of the entire study. The amount of the compensation must not be coercive. The informed consent must indicate that compensation for subjects who withdraw early or are removed from the study by the investigator will be pro-rated accordingly. The UNTHSC legal counsel recommends that the following statement also be included: “As applicable, reimbursement to you may be withheld and credited to any outstanding debts you may have with the University of North Texas Health Science Center at Fort Worth or the State of Texas.

10. Identification (full name[s] and 24 hour phone numbers) of the investigator(s) the subject may contact for answers to questions about the research and the research subject's rights, and whom to contact in

the event the subject believed that he or she has sustained a research-related injury. This should include the IRB Chairman.

11. A statement that participation is voluntary, and that the subject may refuse to participate or may withdraw from the research at any time without penalty or loss of benefits to which the subject is otherwise entitled. When appropriate, subjects should be assured that they would still receive standard treatment if they decide not to participate or to withdraw. They should also be assured that a decision not to participate would not adversely prejudice future interactions with the institution; this is particularly important when a dependent relationship exists between subject and investigator, such as physician-patient, employer-employee or faculty student. If withdrawal may be dangerous to a subject, the danger must be explained and the subject should be told not to withdraw without discussing it with the investigator.

12. Sample documents which contain all of the required elements are available from the IRB Coordinator.

SECTION 9.3 LANGUAGE:

The consent form should give a subject sufficient information about the study, its procedures, benefits, risks and alternatives to enable the subject to make an intelligent decision about participation. The form should be written in the second person with language and terminology the subject could be expected to understand (at approximately the 9th grade reading level). It should invite participation and not sound coercive

SECTION 9.4 TECHNICAL ELEMENTS

At the top of the first page, the consent form should indicate the title of the study, name of the P.I. and the name of the institution. Date of consent must be documented. At the end of the consent form there should be statements that the subject will be given a copy of the form and that his/her signature means he or she has read the form and been given a chance to discuss it and ask questions. Spaces should be provided for (a) the signature of the person who consents to participate; and (b) the individual who witnesses the process of obtaining informed consent; and (c) the individual who obtains the consent of the subject

SECTION 9.5 CONSENT FROM GUARDIANS

There may be rare occasions when the responsible family member or other legal guardian of a subject does not live in the same area as the subject. When it is physically impossible for the investigator to obtain consent in person, the consent may be obtained by mail. This must be pre-approved by the IRB

SECTION 9.6 NON-ENGLISH SPEAKING SUBJECTS

Federal regulations require that informed consent information be presented in “language understandable to the subject”. Informed consent must be obtained in the native language if English is not readily understood by a subject. Written translation of the consent form should be available at the outset of a study if it is anticipated that non-English speaking subjects will be enrolled. Non-English speaking subjects may not be excluded from therapeutic studies, i.e., from studies from which they might be expected to benefit, on the basis of language alone.

SECTION 9.7 ADDITIONAL CONSENT INFORMATION FOR DIFFERENT TYPES OF STUDIES

Studies involving blood samples. Blood samples will be obtained by venipuncture. This method involves inserting a needle into a vein in the arm and withdrawing a sample of blood. It is routinely used to obtain blood for physical examinations. Venipuncture is accompanied by minor discomfort at the site of the

needle entry and may result in slight bruising and a feeling of faintness. In this study a trained technician will obtain a 30 ml (about 2 tablespoonfuls) sample of your blood that will be analyzed for…

Studies that involve students or employees, the Institutional Review Board considers UNTHSC employees and students to be special classes of subjects. Their participation must be completely voluntary and must not include incentives such as compensatory time off. If extra course credit is offered, students must also have an alternative, which takes equal, or less effort to complete than would be required for the research study.

All informed consent documents must address the possible recruitment of students and/or employees. The informed consent should indicate that their participation (or non-participation) would in no way affect their academic standing or employment status. Direct or indirect coercion of students and employees to participate may be construed as academic misconduct.

Studies that involve physical risk. The Health Science Center has no facilities or insurance to cover research related injuries. If the study involves physical risk, assess the risk and add the statement "Neither the investigator conducting this study nor the University of North Texas Health Science Center at Fort Worth are able to offer financial compensation nor to absorb the cost of medical treatment should you be injured as a result of your participation in this research. If required, medical care will be made available to you in the case of such an injury, but you (or your private insurer, Medicare, Medicaid or other governmental healthcare program) will be responsible for the expense of any medical care, including hospitalization, that is needed."

To avoid the appearance of coercion, the following statement should be included in all consent documents that involve risk to the subject: "You should know that be signing this form you are neither waiving any of your legal rights nor releasing the principal investigator, the University of North Texas Health Science Center at Fort Worth or any of their respective agents from liability for negligence with respect to the conduct of this study. If you are injured and feel that your injury justifies pursuing a legal remedy, you have the right to do so."

If there is a risk to a fetus, the female participant must be informed of the risk and the methods to be used (such as a pregnancy test) to minimize the risk.

If the study involves drugs, the participants must be given a statement of known side effects, warned about possible drug interactions (including interactions with alcohol), and warned about activities that may be dangerous (such as driving with a drug that has a sedative effect).

Studies that involve psychological risk. The principles that apply to studies that involve psychological risk or mental stress are similar to those that involve physical risk. Participants should be informed of the risk and told that treatment will not be provided. They should be given the names and telephone numbers of agencies that may alleviate their mental concerns, such as a crisis hot line. If the principal investigator or the faculty sponsor of a student investigator is qualified to treat mental health problems, that person may be listed as a resource.

Studies on sensitive topics. Participants should be told that some of the questions are of a personal or sensitive nature and should be given examples of the topics or questions. They should also be told that they may skip a question if they do not wish to answer it. If questionnaires or interviews may generate reports of child physical or sexual abuse, the participant must be informed that the researcher is legally required to report this information to Child Protective Services. (See the information under item 6 of the synopsis and the Use and Disclosure of PHI for which an Authorization is not required. If the questionnaire or interview may generate reports that the participant plans to harm him or herself or others, the participant must be told that the investigator is ethically required to report that information the local police department. This information about the legal obligations to report abuse and threats of harm to oneself or others may be omitted if the responses are anonymous.

In the event that the Privacy rule is more restrictive than the procedures described in the consent requirements, the more restrictive rule must be followed.

Studies using deception. Deception should be employed only when there are no viable alternative procedures. Where deception is a necessary part of an experiment, the IRB will generally require that a preliminary consent be obtained, in which the investigator informs the subject that the experiment cannot be described fully in advance. After the experiment, the subject should be informed of the deception and its purpose. We recognize that there are rare instances in which no consent can be obtained or debriefing done. Deception requires that a PI get formal approval of a waiver of informed consent, due to the initial consent being used.

Studies with audio or video recordings. Participants must be told: (a) that the interviews or sessions will be audio or videotaped; (b) that the cassettes will be coded so that no personally identifying information is visible on them; (c) that they will be kept in a secure place (e.g., a locked file cabinet in the investigator's office); (d) that they will be heard or viewed only for research purposes by the investigator and his or her associates; and (e) that they will be erased after they are transcribed or coded. If you wish to keep the recordings because of the requirements of your professional organization with respect to data or because you may wish to review them for additional analyses at a later time, the statement about erasing them should be omitted and you should state that they will be retained for possible future analysis.

If you wish to present the recordings at a convention or to use them for other educational purposes, you should get special permission to do so by adding, after the signature lines on the consent form, the following statement, "We may wish to present some of the tapes from this study at scientific conventions or as demonstrations in classrooms. Please sign below if you are willing to allow us to do so with the tape of your performance." And add another signature line prefaced by, "I hereby give permission for the video (audio) tape made for this research study to be also used for educational purposes." This procedure makes it possible for a participant to agree to being taped for research purposes and to maintain the confidentiality of the information on that tape.

Studies with monetary or other compensation. The amount and type of the stipends or other compensations and the requirements to earn them must be clearly specified. Write this part of the consent form as if it were a contract.

SECTION 9.8 DOCUMENTATION OF INFORMED CONSENT

Informed consent must be documented by the use of a written consent form reviewed and approved by the IRB and signed by the subject or subject's legally authorized representative. A copy must be given to the subject or person signing the form. It is assumed that the consent form is only part of the total consent process in which the investigator, perhaps using the written consent form as an outline, describes all facets of the study and answers the subject's questions. The investigator is responsible for insuring that research subjects understand the research procedures and risks. Failure of the subjects to ask questions should not be construed as understanding on the part of the subject.

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SECTION 9.9 NEW FINDINGS

It is the Principal Investigator’s responsibility to report new findings to the IRB **immediately.** If the information may affect a subject’s willingness to begin or continue participation in a research study, the informed consent must be modified accordingly. New findings includes information reported by the sponsor of the research, periodic reports by a data and safety monitoring board, announcement by the Food and Drug Administration and publications in medical and other scientific journals.

SECTION 9.10 DISTRIBUTION OF INFORMED CONSENT FORMS

A signed copy of the consent form must be given to the subject. The original copy must be retained in the investigator's file. If the subject is a patient, a copy of the signed consent form must be placed in the subject's hospital or clinic record.

SECTION 9.11 WAIVER OF WRITTEN INFORMED CONSENT

Principal Investigators may request that the use of consent form be **waived** if:

1. The only record linking the subject and the research would be the consent document and the principal risk would be the potential harm resulting from a breach of confidentiality;
2. The research presents no more than minimal risk of harm to subjects;
3. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
4. The research could not practicably be carried out without the waiver;
5. Whenever appropriate, the subjects will be provided with additional pertinent information after participation;
6. The research is to be conducted for the purpose of demonstrating or evaluating:
    a. Federal, state or local benefit or service programs which are not themselves research programs;
    b. Procedures for obtaining benefits or services under these programs; or
    c. Possible changes in or alternatives to these programs or procedures.

Reasons for request that a written consent be waived should be explicitly stated in a cover memo accompanying the research proposal and protocol. When the documentation requirement is waived or altered, the IRB may still require the research investigator to provide subjects with a written statement regarding the research. Any other consent waiver than those mentioned here may be given only upon recommendation of the IRB and approval by the President of the Health Science Center.

SECTION 9.12 WAIVER OF INFORMED CONSENT

The IRB may waive the requirements for obtaining written informed consent or approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent listed above, provided that all of the following four conditions are met:

1. The research involves no more than minimal risk to the subjects;

2. The waiver or amendment will not adversely effect the rights and welfare of the subjects;

3. The research could not practicably be carried out without the waiver or amendment; and

Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

SECTION 9.13 RECORDS RETENTION REQUIREMENTS FOR SUBJECT CONSENT FORMS/PHI AUTHORIZATION FORMS

FDA regulations require investigators to retain records for a specified time period. For investigational new drug (IND) studies (and medical food and food additive studies), records are to be maintained for two years following the date of marketing application approval for the drug for the indication for which it was being investigated. If no application is filed, or if the application is not approved for the indication, the records are to be retained for two years after the investigation (i.e., the IND) is discontinued, and FDA is notified of that fact. For device studies, records are to be maintained for two years after the later of the following

dates: the date on which the investigation is terminated or completed, or; the date that the records are no longer required to support a pre-market approval application or a notice of completion of a product development protocol.

To comply with FDA record retention requirements, clinical investigators should arrange with study sponsors to be kept informed of the status of the application for their respective studies.

For non-FDA studies, all records must be maintained for a *minimum of 5 years* after completion of the study.

SECTION 9.14 FDA INSPECTION OF STUDIES

The Principal Investigator is responsible for sending the IRB copies of all correspondence pertaining to FDA inspection of studies. This includes Form FDA 483 (Inspectional Observations), and all other related follow-up correspondence, both to and from the FDA. This correspondence must be sent to the IRB within five working days of receipt/transmittal.

SECTION 9.15 NON-COMPLIANCE WITH IRB REQUIREMENTS

Federal regulations require that all documentation for projects involving human subjects be completed accurately and submitted in a timely manner. Failure to comply with this request will result in suspension or termination of IRB approval. If IRB approval is suspended or terminated, the IRB Chair will notify the study sponsor and the FDA or OHRP, as applicable, in writing within five working days.

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SECTION 10: CONTINUING REVIEW

SECTION 10. 1 INTRODUCTION

As a condition of project approval, the Institutional Review Board provides for the continuing review of all research projects involving the use of human subjects at least annually, and appropriate to the degree of risk, more frequently. The Principal Investigator is required to complete IRB Form 4 (Continuing Review and Final Report Form) and explain any changes in protocol or problems encountered since the last review. **An integral part of this process is reassessment of the risk/benefit relationship.**

SECTION 10.2 PROCEDURES

Approximately 90 days prior to the expiration date of IRB approval, the IRB administrative staff will forward an IRB Form 4 to the Principal Investigator.

Upon return of the completed IRB Form 4 to the IRB office, the administrative staff will collate the following information for inclusion in the packets to be distributed to each IRB member approximately two weeks prior to the next convened meeting:

- IRB Form 4 (Continuing Review and Final Report Form)
- Copy of proposed (if revised) and/or "old" (approved) informed consent/informed assent documents
- Copy (if changed significantly from last convened review) of protocol synopsis
- Any applicable supplementary materials, including recent DSMB reports

The IRB Chair and Vice Chair, in addition to receiving each of the items listed above, will also receive:

Copy of most recent version of drug company protocol or grant application
Copy of most recent version of protocol synopsis
Copy of most recent Investigator's Brochure
NOTE: Upon receipt of their packets, members of the IRB are encouraged to contact the administrative staff for copies of any additional materials they will require to conduct their review.

SECTION 10.3 REVIEW

Continuing IRB review of research must be substantive and meaningful. Each project will be presented and discussed individually. Each project will be voted upon individually. There are times when the risks associated with a particular project are such that continuing review should take place more frequently than annually. In these cases, the IRB will specify that the Principal Investigator report to the IRB at a more frequent interval (e.g. 6 months).

Projects that have been assessed as very high risk (e.g. 3 month continuing review schedule) will require verification from sources other than the investigators that no material changes have occurred since previous IRB review.

It continues to be the responsibility of the IRB during the continuing review process to determine (as was done during the initial review) whether or not vulnerable populations (e.g. children, pregnant women) may participate in the research.

It is important to note that it is the policy of the UNTHSC IRB to conduct continuing review only at convened meetings (rather than under an expedited review procedure), regardless of the initial type of review (e.g. expedited) or current disposition of the project (e.g. closed to enrollment and subjects receiving follow-up only). This policy permits the convened IRB to review all informed consent documents and, as applicable, determine whether subjects already enrolled should be provided with additional information that was not provided to them when they first enrolled.

SECTION 10.4 AMENDMENTS TO PROTOCOLS

Amendments to protocols or consent/authorization forms must be requested in writing, and reviewed and approved by the IRB prior to making any changes in study procedures. Requests must describe what modifications are desired, why the changes are required, and if the changes pose any additional risks to the subjects. Minor changes to the protocol or consent forms (those that do not increase the risk or decrease the potential benefit to subjects) may be administratively approved according to 45 CFR 46.110(b)(2). Most amendments will qualify for expedited review. Changes considered to be more than minor must be reviewed at a convened meeting of the IRB. All amendments are reported to the IRB, and those that are more than minor are discussed and approved by IRB at a convened meeting. It is important that the protocol and consent of the study as it is being conducted, and the authorization to use and disclose the PHI correspond to the current protocol and consent/authorization approved by the IRB.

The UNTHSC IRB uses the expedited review procedure to review minor changes in previously approved research when these changes involve no more than minimal risk, or do not increase the risk level of the research. These changes are processed as amendments to a project. Typical changes include changes in key personnel, changes in sample size, an addition of a questionnaire, a change in the compensation schedule, an addition of a site, etc.

SECTION 10.5 ADVERSE EVENT REPORTING

IRB Forms 3a (Serious Adverse Event Report for SAEs at UNTHSC) and IRB Form 3b (Serious Adverse Event Report for SAEs at Other Sites) should be used in reporting all deaths and life-threatening or unanticipated medial or psychological incidents that occur involving human subjects during investigational procedures or treatments.

Within 24 hours, an initial report must be filed electronically of any serious adverse event which the investigator feels **is related** to the study protocol. The FDA defines a serious adverse event 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 experience includes any experience that is fatal or life-threatening, is permanently disabling or requires or prolongs inpatient hospitalization. This report must contain the following information:

IRB Project #
Principal Investigator
Project Title
Subject's Initials, Gender and Age
Date and Time of Adverse Event
Brief Description of Adverse Event

What Event Resulted In:

- Death
- Life-Threatening Situation
- Hospitalization or Prolonged Hospitalization
- Severe or Permanent Disability
- Other

This information should be electronically submitted to Debbie Ceron either via Groupwise (dceron) or e-mail (dceron@hsc.unt.edu).

Within 10 working days, a detailed report (IRB Form 3a) must also be completed and forwarded, along with supporting documentation, to the IRB. IRB Form 3b should be used to report adverse events that have occurred at other sites.

SECTION 10.6 PRINCIPAL INVESTIGATOR NOTIFICATION

After the convened IRB meeting, the disposition of the project is relayed to the Principal Investigator by IRB Form 2 (Board Action Form). Any stipulations and/or determinations will also be relayed. The informed consent approved at the convened meeting will be stamped with the IRB stamp and the date of the IRB meeting.

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SECTION 11 ADVERTISING FOR HUMAN SUBJECT PARTICIPATION IN RESEARCH

SECTION 11.1 APPROVAL OF RECRUITMENT MATERIAL

Advertisements (including posters, pamphlets, institutional e-mail messages, newspaper ads, etc.) soliciting volunteers for research must have IRB approval. This approval may be obtained in one of three ways:

1. Materials may be submitted with the initial proposal for concurrent approval by the IRB.

2. Materials may be submitted following approval of the initial proposal. In this case, the materials should be submitted as an amendment to the ongoing study. When the materials are easily compared to the consent, the materials will be reviewed using expedited review procedures. When the comparison is not obvious or other complicating issues are involved, in the opinion of the IRB chair or designated representative, the materials will be reviewed at a convened meeting of the IRB.

3. General advertisements (not attached to a specific study) must also be submitted for approval by the IRB. In this case, the following rules will apply:

    a. The solicitation must be general in nature, and not refer to any specific study not already approved by the IRB.

    b. The solicitation must not contain any promises or commitments to the potential subjects.

    c. Information collected must be restricted to that necessary for subject identification only (e.g., name, address, topic of interest, etc.). Information must be kept confidential and destroyed when no longer needed. Potential subjects must be advised of their right to confidentiality and the ability to have their name removed from the list.

d. Potential subjects must be advised that placing their name on the list does not constitute any commitment by or to them, and that their actual participation in a particular study will be subject to their approval and consent.

e. Potential subjects must be advised that they may contact the IRB Chair if they have any problems or questions.

f. The solicitation will be subject to all of the restrictions and requirements of any other solicitation.

g. Approval of general advertisements will be performed by full board review only.

The submission to the IRB should include the advertisement, copies of all recordkeeping forms, and all handouts.

SECTION 11.2 INSTITUTIONAL REQUIREMENTS FOR RECRUITMENT MATERIAL

All advertisements must contain the following information:

- The advertisement must indicate that the research study is being sponsored by the University of North Texas Health Science Center at Fort Worth.
- The advertisement must clearly indicate that potential subjects will be volunteering for a research study.
- The following information may be included in advertisements:
- The name and address of the Principal Investigator or contact person;
- The condition under study and/or the purpose of the research;
- A summary of the criteria used to determine eligibility for the study;
- A brief list of participation benefits, if any (e.g. a no-cost health examination);
- The time or other commitment required of the subjects.

Advertisements must not:

Contain any claims that the drug, biologic or device is safe or effective for the purposes being studied, or that the test article is known to be equivalent or superior to any other drug, biologic or device.

Should not promise “free medical treatment” when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be compensated for their time and travel expenses, but must not emphasize the amount of the compensation, by such means as dollar signs or larger or bold type.

Must not use terms such as “new treatment”, “new medication” or “new drug” without explaining that the test article is investigational.

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SECTION 12: EMERGENCY USE OF EXPERIMENTAL DRUGS OR DEVICES

SECTION 12.1 EMERGENCY USE WITH A SINGLE SUBJECT

The Institutional Review Board recognizes that there are conditions that require emergency approval of experimental drugs or devices when a subject's welfare is at stake.

The emergency use of an experimental drug or device for benefit of a single subject may be approved without delay by the Chair of the Institutional Review Board provided a life-threatening situation exists. The following conditions must exist for a situation to be considered an emergency (21 CFR 56.104(c)):

1. The subject is in a life-threatening condition that needs immediate treatment.
   A life-threatening disease is defined as a stage of disease in which there is a reasonable likelihood that death would occur within a matter of months or in which premature death is likely without early treatment.
2. No acceptable alternative for treatment of the subject is available.
3. Because of the immediacy of the need to use the drug or device, there is no time to use existing procedures to obtain IRB and FDA approval.

Approval can be obtained whenever a subject does not meet all eligibility criteria for an existing IRB approved protocol, or when an approved research protocol does not exist. However, in this case the drug or procedure **can be used only once**. Additional uses will require the submission of a formal research protocol for IRB approval. It is important to note that the requirement to obtain informed consent **prior** to the subject's participation **is not waived** (see Informed Consent in Cases of Emergency Use and Exception from Informed Consent for Studies Conducted in Emergency Settings for the only legal exceptions to this rule).

To request emergency approval, phone, fax or e-mail the Chair of the IRB prior to use of the drug or device. This should be followed-up **within five working days** after the use of the experimental drug or device by a letter detailing the following:

1. The subject's name and age.
2. Physical condition, to include all current diagnoses.
3. Listing of previous treatment options attempted and the results.
4. Listing of any other concurrent medications or procedures.
5. Any additional documentation justifying the use of the experimental drug or device including any additional documentation of non-available alternative therapy.
6. IND/IDE and the name of the sponsor that provided the drug or device.
7. Where the subject was treated.
8. Procedures, duration and dosage of drug or device used.
9. A copy of the signed consent form. The consent form must meet the criteria normally required of an IRB project.
10. The name of a physician uninvolved in the subject's care who concurs that the drug or device was needed for a life-threatening situation.

SECTION 12.2 EXTREME EMERGENCY USE OF EXPERIMENTAL DRUGS OR DEVICES

In extreme emergencies (minutes or hours), an experimental drug or device may be used without prior IRB approval provided:

The investigator and an uninvolved physician (who is not otherwise participating in the clinical investigation or procedure) certify in writing in the subject's medical record that the drug or device is needed for a life-threatening (minutes or hours) situation.

The subject or the subject's legal guardian signs a consent form (that meets the criteria normally required of an IRB project) **prior** to the subject's participation .

If an IND/IDE exists, the sponsor is notified of the emergency use of the drug or device.

If an IND/IDE does not exist, the FDA is notified of the emergency use of the drug or device.

A letter describing the situation and a copy of the signed consent form are submitted to the IRB **within five working days** after the use of the experimental drug or device.

SECTION 12.3 INFORMED CONSENT IN CASES OF EMERGENCY USE

In all cases of emergency use, an Informed Consent is required to be signed by the subject or the subject's legal representative prior to the subject's participation. However, an informed consent is not required (21 CFR 50.23) if the investigator and a physician who is not otherwise participating in the clinical investigation or procedure certifies in writing, **before the use of the experimental drug or device:**

1. The human subject is confronted by a life-threatening situation necessitating the use of the experimental drug or device; and
2. Informed consent cannot be obtained from the subject because of an inability to communicate with or legally obtain effective consent from the subject; and
3. Time is not sufficient to obtain consent from the subject's legal representative; and
4. No alternative method or approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

When this exception to informed consent is used, the written certification must be submitted to the IRB **within five working days** after the use of the drug or device.

SECTION 12.4 EXCEPTION FROM INFORMED CONSENT FOR STUDIES CONDUCTED IN EMERGENCY SETTINGS

Federal regulations provide a narrow exception to the requirement for informed consent from each human subject, or his or her legally authorized representative, prior to initiation of an experimental intervention. The exception applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention but who cannot give informed consent because of their life-threatening medical condition, and who do not have a legally authorized person to represent them. This is not the same as the emergency use of an experimental drug or device for benefit of a single patient (see Emergency Use of Experimental Drugs or Devices and Informed Consent in Cases of Emergency Use). The intent of these regulations is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies. However, because of special regulatory limitations relating to research involving fetuses, pregnant women, human *in vitro* fertilization, and prisoners, these regulations are inapplicable to those categories of research.

Due to the significant legal and ethical implications involved, the following conditions and procedures must be followed **exactly:**

a. Research Subject to FDA Regulations: The IRB responsible for the review, approval and continuing review of the research activity has approved both the activity and a waiver of informed consent and found and documented:

1. That the research activity is subject to regulations codified by the FDA at Title 21 CFR Part 50 and will be carried out under an FDA investigational new drug application (IND) or an FDA investigational device exemption (IDE), the application for which has clearly identified the protocols that would include subjects who are unable to consent, and
2. That the requirements for exception from informed consent for emergency research detailed in 21 CFR Section 50.24 have been met relative to those protocols, or

b. Research Not Subject to FDA Regulations: The IRB responsible for the review, approval and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research is not subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented and reported to the OPRR that the following conditions have been met relative to the research:

1. 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.
2. Obtaining informed consent is not feasible because:

i. The subjects will not be able to give their informed consent as a result of their medical condition;

ii. The intervention involved in the research must be administered before consent from the subjects' legally authorized representatives is feasible; and

iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.

3. 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;

i. 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

ii. 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.

4. The research could not practicably be carried out without the waiver.
5. 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.
6. The IRB has reviewed and approved informed consent procedures and an informed consent document in accord with Sections 46.116 and 46.117 of 45 CFR Part 46. These procedures and the informed consent document 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.
7. 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;

i. 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;

ii. 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;

iii. Establishment of an independent data monitoring committee to exercise oversight of the research; and

iv. 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 he or she objects 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.

To comply with FDA record retention requirements, clinical investigators should arrange with study sponsors to be kept informed of the status of the application for their respective studies.

For non-FDA studies, all records must be maintained for a *minimum of 5 years* after completion of the study.

SECTION 12.5 FDA INSPECTION OF STUDIES

The Principal Investigator is responsible for sending the IRB copies of all correspondence pertaining to FDA inspection of studies. This includes Form FDA 483 (Inspectional Observations), and all other related follow-up correspondence, both to and from the FDA. This correspondence must be sent to the IRB within five working days of receipt/transmittal.

SECTION 12.6 NON-COMPLIANCE WITH IRB REQUIREMENTS

Federal regulations require that all documentation for projects involving human subjects be completed accurately and submitted in a timely manner. Failure to comply with this request will result in suspension or termination of IRB approval. If IRB approval is suspended or terminated, the IRB Chair will notify the study sponsor and the FDA or OHRP, as applicable, in writing within five working days.

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SECTION 13: SPECIAL PROCEDURES FOR PROVIDING ADDITIONAL PROTECTIONS FOR PREGNANT WOMEN, HUMAN FETUSES, AND NEONATES INVOLVED IN RESEARCH

SECTION 13.1 GENERAL GUIDANCE

In addition to the responsibilities prescribed for the IRB, the Board shall follow special procedures with respect to vulnerable populations, in this case the procedures provide additional safeguards in research activities involving, pregnant women, human fetuses, and neonates. This section is intended to follow the guidelines set forth in Subpart B of 45 CFR 46.201-207. Investigators must supply sufficient justification for inclusion of pregnant women, fetuses, or neonates in research activities.

SECTION 13.2 DEFINITIONS

"Pregnancy" encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the presumptive signs of pregnancy, such as missed menses, until the results of pregnancy testing are negative or until delivery.

"Fetus" means the product of conception from implantation until delivery.

"**Neonate"** means a newborn.

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SECTION 14: SPECIAL PROCEDURES FOR PROVIDING ADDITIONAL PROTECTIONS FOR HUMAN SUBJECTS WHO ARE PRISONER

The Institutional Review Board at the University of North Texas Health Science Center at Fort Worth *does not review or approve* research involving arrested or incarcerated persons.

The word "prisoner" is defined in 45 CFR 46.30(c) as follows: "Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing."

If a research subject is subsequently arrested and incarcerated after enrollment on an IRB-approved study, notify the IRB immediately.

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SECTION 15: SPECIAL PROCEDURES FOR PROVIDING ADDITIONAL PROTECTIONS FOR HUMAN SUBJECTS WHO ARE CHILDREN

SECTION 15.1 GENERAL CONDITIONS

All research involving children and minors must comply with the protections to human subjects at 45 CFR 46.401-409. The guidelines apply to all research, including biomedical and behavioral research, and even to research exempt from full IRB review. The guidelines require that the inclusion of children must be justified based on the benefits, risks (minimal or greater than minimal), and the amount of discomfort inherent in the proposed research. At the same time, any exclusion of children must be justified based on scientific, ethical or legal grounds (see below).

Parental permission is required for most studies and must be documented in a written consent form. The child's assent to participate should be obtained (if the child is seven years of age or older) and documented in a pediatric assent form, which must be written in language that can be understood by a child. The IRB Coordinator can provide you with sample documents to assist you in developing these consent/assent forms.

SECTION 15.2 DEFINITIONS

1. **"Children"** are persons who have not attained the legal age for consent/authorization to treatments or procedures involved in research or clinical investigations, under the applicable law of the jurisdiction in which the research or clinical investigations will occur.
2. **"Assent"** means the child's affirmative agreement to participate in research or clinical investigation. Mere failure to object may not constitute assent.
3. **"Permission"** means the agreement of parent(s) or guardian to the participation of the child in the research or clinical investigation.
4. **"Parent"** means a child's biological or adoptive parent.
5. **"Guardian"** means an individual who is authorized under state or local law to consent/authorization on behalf of a child to general medical care when general medical care includes participation in research.

SECTION 15.3 SEVEN ETHICAL AND SCIENTIFIC RATIONALES FOR EXCLUDING CHILDREN FROM RESEARCH PROJECTS*

NIH has named seven acceptable reasons to exclude children from a study:

1. The research topic is irrelevant to children (e.g., the medical or social condition under study is found only in older persons).
2. There are laws or regulations barring inclusion of children.
3. The knowledge being sought is already available for children or will be obtained from another ongoing study, and an additional study would be redundant (researchers must provide the IRB with sound scientific justification).
4. A separate age-specific study in children is warranted and preferable, for example, because of the relative rarity of a condition in children compared to adults; extraordinary effort would be needed to include children, or considerable effort has been spent to assemble the adult population under study; or the number of children is limited because the majority are already accessed by a nationwide pediatric disease research network. Issues of study design may preclude direct applicability of a hypothesis and/or intervention to both adults and children; such issues include differences in cognitive, developmental, or disease stages, or different age-related metabolic processes. Exclusion may be permitted in such cases, but researchers may be asked to consider taking these differences into account in the study design or expanding the hypothesis to include children.
5. Insufficient data are available to judge the risk to participating children. In this case, one of the research project objectives could be to obtain sufficient adult data to make this judgment.
6. The study involves follow-up on a previous study of adults.
7. Other special cases are found acceptable by review groups and the Director of the NIH.

* Adapted from NIH policy and guidelines written by Moira Keane, University of Minnesota

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SECTION 16: SPECIAL PROCEDURES FOR PROVIDING ADDITIONAL PROTECTIONS FOR HUMAN SUBJECTS WHO ARE EMPLOYEES OR STUDENTS

The Institutional Review Board considers UNTHSC employees and students to be special classes of subjects. Their participation must be completely voluntary and must not include incentives such as compensatory time off. If extra course credit is offered, students must also have an alternative that takes equal or less effort to complete than would be required for the research study.

All informed consent documents must address the possible recruitment of students and/or employees. The informed consent should indicate that their participation (or non-participation) would in no way affect their academic standing or employment status.

Direct or indirect coercion of students and employees to participate may be construed as academic misconduct.

SECTION 17: SPECIAL PROCEDURES FOR PROVIDING ADDITIONAL PROTECTION TO ADULTS WHO LACK DECISION-MAKING CAPACITY

Special procedures for IRB review and approval apply to research activities involving potential research subjects who, for a wide variety of reasons, are incapacitated to the extent that their decision-making capabilities are diminished or absent. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems. Conversely, individuals with these problems should not be presumed to be cognitively impaired. Investigators must justify the inclusion of subjects with impaired decision-making capacity and clearly indicate how the subject rights will be protected.

The guidelines upon which this requirement is based may be reviewed in a document produced by the Office for Human Research Protection (OHRP) as "Points to Consider." The OHRP intends that they be used by IRBs and investigators in their effort to protect research subjects.

Generally, cognitively impaired potential or actual research subjects may not understand the difference between research and treatment or the dual role of the researcher. Therefore, when appropriate, it is essential that the consent/authorization process clearly indicate the differences between individualized treatment (e.g., special education in classroom settings) and research.

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SECTION 18: USE OF PROTECTED HEALTH INFORMATION FOR RESEARCH POLICY

SECTION 18.1 APPLICABILITY

This policy is applicable to all University of North Texas Health Science Center (UNTHSC) faculty, staff, and students involved in research activities.

SECTION 18.2 UNTHSC PRIVACY POLICY

This policy supplements the requirements of the UNTHSC “Protected Health Information Privacy Policy.” The purpose of this policy is to describe the procedure for conducting research involving Protected Health Information (hereinafter referred to as PHI). The federal “Health Insurance Portability and Accountability Act” (“HIPAA”) Privacy Rule directly applies to “covered entities”: health plans, health care clearinghouses, and health care providers who transmit health information electronically. Under HIPAA, UNTHSC is a “covered entity”. Researchers who obtain Protected Health Information from covered

entities (whether inside or outside of UNTHSC) to conduct research must comply with the HIPAA rules pertaining to use and disclosure of PHI for research.

SECTION 18.3 DEFINITIONS

Disclosure: the release, transfer, provision of access to, or divulging in any other manner of information outside the entity holding the information.

Protected Health Information ("PHI"): individually identifiable health information transmitted or maintained in any form or medium, including oral, written, and electronic communications. Individually identifiable health information relates to an individual's past, present or future health status or condition, furnishing health services to an individual or paying or administering past, present or future health care benefits to an individual. Information is considered PHI where the individual is identified or there is a reasonable basis to believe the information can be used to identify an individual.

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes.

SECTION 18.4 USE AND DISCLOSURE OF PHI FOR RESEARCH

In the course of conducting research, researchers may obtain, create, use, and/or disclose individually identifiable health information if done in accordance with this policy and the HIPAA Privacy Rule. As a general rule, a researcher must obtain a patient authorization from all participants in research prior to the internal use or external disclosure of PHI for any research related purpose that is not otherwise permitted or required under this Policy. However, patient authorization is not needed under limited circumstances set forth in the HIPAA Privacy Rule.

SECTION 18.4.1 RESEARCH USE/DISCLOSURE WITH INDIVIDUAL AUTHORIZATION

1. The Privacy Rule permits covered entities to use or disclose Protected Health Information for research purposes when a research participant authorizes the use or disclosure of information about his or her health information.
2. The IRB will provide an Authorization template that complies with HIPAA requirements. The researcher must complete the Authorization template and submit it to the IRB for prior review and approval.
3. To use or disclose Protected Health Information with authorization by the research participant, the covered entity must obtain an authorization that satisfies the Privacy Rule. The Privacy Rule has a general set of authorization requirements that apply to all uses and disclosures, including those for research purposes. The authorization must contain each of the following items:
    a. A description of the extent to which PHI will be used or disclosed.
    b. A specific description of the PHI to be disclosed; the person(s) that will be using or disclosing the PHI; the person(s) authorized to receive the PHI; the purpose(s) for which the PHI will be used/disclosed.
    c. A statement as to whether the PHI will be subject to use by or re-disclosure to entities not covered by the HIPAA Privacy Rule.
    d. The expiration date or expiration event for use or disclosure of the PHI.
    e. A statement of the patient's right to revoke the authorization.
    f. A statement that treatment, payment, enrollment or eligibility for benefits cannot be conditioned upon the patient's signing the authorization. However, participation in research may be conditioned on a signed authorization, including treatment protocols.

g. A statement that the PHI that is disclosed may potentially be re-disclosed and may no longer be protected under HIPAA.
h. The individual's signature (or that of his/her authorized representative) and date. The individual must be provided with a copy of the signed authorization.

SECTION 18.4.2 SPECIAL PROVISIONS APPLY TO RESEARCH AUTHORIZATIONS

Unlike other authorizations, an authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the "end of the research study;"

An authorization for the use or disclosure of Protected Health Information for research may be combined with consent to participate in the research, or with any other legal permission related to the research study.

SECTION 18.5 INDIVIDUAL'S ACCESS TO RESEARCH INFORMATION

As a general rule, individuals who participate in research have a right to access their own PHI that is maintained in a Designated Record Set of a Covered Entity. Designated Record Sets are those that are used to make treatment, payment and healthcare operations decisions about individuals. In general, research data sets are not among the "Designated Record Sets" of a Covered Entity. However, the Covered Entity's Designated Record Sets include the individual's medical records, payment records, etc. All data about an individual that is generated in clinical research and entered into the individual's medical or financial records at the Covered Entity are that individual's PHI.

Individuals participating in research protocols that include treatment (for example, a placebo controlled clinical trial) may be temporarily denied access to their PHI obtained in connection with that research protocol, provided that:

i. The PHI was obtained in the course of the research;
ii. The individual agreed to the denial of access in the Research Authorization;
iii. The research remains in process; and
iv. The individual's rights to access such PHI are re-instated once the research study has concluded.

SECTION 18.6 INDIVIDUAL'S REVOCATION OF AUTHORIZATION

a. As a general rule, an individual may revoke his/her authorization, in writing to the Principal Investigator, at any time. The revocation will be applicable to the protocol or protocols specified by the individual. However, the researcher may continue to use and disclose, for research integrity and reporting purposes, any PHI collected about the individual pursuant to a valid authorization before it was revoked.
b. The Principal Investigator shall maintain a copy of each written revocation and shall report them to the IRB at the time of continuing review.

SECTION 18.7 RESEARCH USE/DISCLOSURE WITHOUT AUTHORIZATION

To use or disclose Protected Health Information without authorization by the research participant, a covered entity must obtain one of the following:

SECTION 18.7.1 DOCUMENTED IRB APPROVAL

Documentation that an alteration or waiver of research participants' authorization for use/disclosure of information for research purposes has been approved by an Institutional Review Board (IRB) or a Privacy Board. At UNTHSC, any such waiver of authorization must be approved by the UNTHSC IRB. A covered entity may use or disclose protected health information for research purposes pursuant to a waiver of authorization by an IRB, provided it has obtained documentation of *all* of the following:

- Identification of the IRB and the date on which the alteration or waiver of authorization was approved;
- A statement that the IRB has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Privacy Rule;
- A brief description of the Protected Health Information for which use or access has been determined to be necessary by the IRB;
- A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
- The signature of the chair or other member, as designated by the chair of the IRB.

The following three criteria must be satisfied for an IRB to approve a waiver of authorization under the Privacy Rule:

a. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    - an adequate plan to protect the identifiers from improper use and disclosure;
    - 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
    - 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 project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
b. The research could not practicably be conducted without the waiver or alteration; and
c. The research could not practicably be conducted without access to and use of the Protected Health Information.

SECTION 18.7.2 PREPARATORY TO RESEARCH

To allow use of this method, the covered entity must require representations from the researcher, either in writing or orally, that the use or disclosure of the Protected Health Information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any Protected Health Information from the covered entity, and representation that Protected Health Information for which access is sought is necessary for the research purpose.

SECTION 18.8 RESEARCH ON PHI OF DECEDENTS

This alternative requires representations from the researcher, either in writing or orally, that the use or disclosure being sought is solely for research on the Protected Health Information of decedents, that the Protected Health Information being sought is necessary for the research, and, at the request of the covered entity, documentation of the death of the individuals about whom information is being sought.

SECTION 18.9 DE-IDENTIFIED HEALTH INFORMATION

Individual health information that conforms to the HIPAA definition of "de-identified" is exempt from HIPAA and may be used or disclosed for research purposes without an authorization or waiver of authorization or data use agreement. Researchers must provide documentation to the IRB that the health information has been de-identified by one of the following two methods:

(a) Method 1: Health information is de-identified if a set of specific identifiers is deleted before the information is released by the covered entity to the researcher. These identifiers are the following:

- Names
- Address (including all geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geo-codes, except for the initial three digits of most zip codes)
- All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, and date of death
- All ages over 89 and all elements of dates (including year) indicative of age over 89, except that ages over 89 may be aggregated into a single category of "age 90 or older"
- Telephone number
- Fax number
- E-mail address
- Social security number
- Medical record number
- Health plan beneficiary number or account number
- Certificate/license number
- Vehicle identifiers and serial numbers including license plate numbers
- Universal Resource Locators (URLs)
- Internet Protocol (IP) address numbers
- Biometric indicators such as fingerprints or voiceprints
- Full-face photographic images and any comparable images
- Any other uniquely identifying number, characteristic, or code that could be used to identify the individual

Also, neither the covered entity nor the researcher has a reasonable basis to believe that the information can be used alone or in combination with other information to identify an individual.

(b) Method 2: The second method of de-identifying under HIPAA allows a person with appropriate knowledge and experience to apply generally acceptable statistical and scientific principles and methods for rendering information not individually identifiable to make a determination that there is a very small risk that the information could be used by others to identify a subject of the information, and documents the methods and results

SECTION 18.10 LIMITED DATA SETS WITH A DATA USE AGREEMENT

This alternative involves a data use agreement entered into by both the covered entity and the researcher, pursuant to which the covered entity may disclose a limited data set to the researcher. A limited data set excludes specified direct identifiers of the individual or of relatives, employers, or household members of the individual. The data use agreement must:

- Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or disclosure that would violate the Rule if done by the covered entity;
- Limit who can use or receive the data; and
- Require the recipient to agree to the following:
- Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
- Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
- Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware;
- Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
- Not to identify the information or contact the individual.

Under the limited data set approach, the following identifiers of the individual, relatives, employers, and household members of the individual must be removed before the data is released by the covered entity to the researcher:

- Names
- Postal address information other than city, State, and zip code
- Telephone and fax numbers
- E-mail address, URLs and IP addresses
- Social security number
- Medical record numbers, health plan beneficiary numbers and other account numbers
- Device identifiers and serial numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plates
- Full face photos and other comparable images
- Biometric identifiers including fingerprints and voiceprints

The IRB has templates for Internal and External Data Use Agreements.

SECTION 18.11 PUBLICATIONS OR PUBLIC PRESENTATIONS

PHI from research may not be included in presentations or publications of any type unless explicitly permitted by either the individual's authorization or the IRB's waiver of authorization and in accord with the terms and conditions of all existing agreements governing how that individual's information may be used including: the terms and conditions of IRB approval of the research protocol, the authorization or waiver of authorization, the informed consent or waiver of informed consent, any data use agreement that has been executed, etc.

SECTION 18.12 TRANSITION PROVISIONS

For Research involving PHI and carried out according to a protocol reviewed and approved by the IRB prior to April 14, 2003:

1. A research study may continue to use or disclose the PHI created or received prior to April 14, 2003 without HIPAA documentation.
2. A research study operating under a waiver of informed consent approved by the IRB prior to April 14, 2003, may continue to create, receive, use, and disclose PHI for the study after April 14, 2003, without an IRB Waiver of Authorization unless the research study subsequently seeks informed consent, in which case an authorization would be required together with the informed consent.
3. If the protocol approved by the IRB before April 14, 2003, required the obtaining of an informed consent, then with respect to any individual who has executed informed consent before April 14, 2003, no additional authorization is required to create, receive, use and disclose that individual's PHI for the approved study.
4. Any research participant for which informed consent is required, any informed consent or reconsent on or after April 14, 2003, must include an authorization for use or disclosure of the subject's PHI. If the research has been previously approved but will be enrolling participants on or after April 14, 2003, the researcher must submit a protocol revision to the IRB in order to include an individual authorization with any informed consent obtained on or after April 14, 2003.

SECTION 18.13 TEXAS MEDICAL PRIVACY ACT.

Enactment of the Texas Medical Privacy Act (added by Acts 2001, 77th Leg.) added Chapter 181 ("Medical Records Privacy") to the Texas Health and Safety Code. Chapter 181 greatly expands the list of entities that will be affected by the HIPAA privacy regulations. Although the HIPAA Privacy Rule narrowly defines "covered entity," Chapter 181 defines "covered entity" to include "any person who…comes into possession of protected health information." The compliance date for Chapter 181 is September 1, 2003.

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SECTION 19 PROCEDURES FOR AUDITING RESEARCH STUDIES INVOLVING HUMAN SUBJECTS

SECTION 19.1 BACKGROUND

The purpose of the IRB audit program is to ensure that research is being conducted appropriately and that all subjects enrolled have been fully informed through a properly conducted informed consent process.

When a study has been approved by the IRB, the protocol and consent forms, along with supporting documentation, provide the template by which a research project is to be conducted. The purpose of an audit is to ensure that the approved plan has been followed, that both local and federal guidelines for the protection of human subjects have been adhered to, and that proper written documentation exists. In addition to ensuring the paperwork is in order, the audit is also to ensure that the process and manner in which subjects are recruited, enrolled, and treated throughout the study is in accord with the principles of the Belmont Report.

SECTION 19.2 OVERVIEW OF AUDIT FRAMEWORK

These guidelines establish a framework within which the UNTHSC IRB will direct and conduct audits.

The purpose is to ensure that audits are conducted in an independent and rigorous manner by establishing requirements for who conducts audits, how they are to be conducted, and how results are to be reported.

1. Foster a culture of continuous improvement by identifying incidents of non-compliance;
2. Assisting investigators in developing their own programs for quality improvement;
3. Act proactively to minimize the need for formal sanctions.

SECTION 19.3 STAGED APPROACH

Three types of audits may be conducted: administrative, random audit, and a for-cause comprehensive audit. The frequency and scope of audits will be determined by the IRB. Random or administrative audits will be conducted at least twice annually with the number of studies to be audited determined by the IRB. This will depend on staff resources and the total number of ongoing studies.

Individual studies may be audited on a more frequent, non-random basis at the direction of the IRB.

SECTION 19.4 ADMINISTRATIVE AUDIT

An administrative audit may be conducted by IRB staff or by an individual IRB member at the direction of the IRB. Administrative audits will be conducted in a random manner, at least twice a year, with the number of studies to be audited determined by the IRB.

The purpose of an administrative audit will be to determine the presence or absence of key documentation, to include:

- Study protocol
- Grant
- Investigators brochure
- Consent forms
- Continuing reviews

- Adverse Event reports

For an administrative audit, the auditor will be appointed by the IRB chair. The auditor will contact the investigator and arrange a time to examine the records. The auditor will determine if the required documentation is present, and that the documentation in use represents the most recent, approved versions. The auditor will determine if there is a signed consent form on file for each subject.

The auditor will prepare a brief report to the IRB indicating whether the required elements are present or absent. The auditor may also make recommendations, including but not limited to, recommending a full audit. This brief report can take the form of a standardized checklist.

SECTION 19.5 RANDOM AUDIT

Because industry sponsored clinical trials are already subject to regular audits by the sponsor and the FDA, the IRB may either elect to rely on those audits or to conduct a separate audit. All other studies are always eligible for a comprehensive audit.

SECTION 19.5.1 APPOINTMENT OF AUDITORS

A full audit team needs to have both sufficient experience and expertise to assess the study in question, and sufficient independence to give a frank and impartial assessment of the study.

A full audit team will consist of two members of the UNTHSC IRB and one staff member. One of the IRB members will be appointed as the team leader. If additional expertise is needed, outside experts may also be asked to participate in the audit process.

Members of the audit team, so far as feasible, should not have a collaborate relationship with the investigator that would create, or could be seen to create, a conflict of interest.

The members of the audit team will be selected by the IRB.

SECTION 19.5.2 PROCEDURE

The audit will begin with a review of the IRB files. Based on this review, the team will determine what additional documentation is needed and what activities need to be conducted at the study site.

The investigator will be contacted and informed of the pending audit. The investigator will be given a list of documents requested by the team, and will provide the team with a list of all subjects enrolled in the study.

As with an administrative audit, the auditors will check for presence or absence of the key documents.

The team will also review any additional documentation according to the strategy developed for the audit.

A subset of subjects will be selected at random by the auditors, and the entire physical record for those subjects will be reviewed.

The audit team will then select subjects at random to interview. The interview will be designed to; assess whether the subject has a full understanding of the study, the associated risks and benefits, and their role and rights in the study. The interview may also assess their level of satisfaction with the study, the IRB, and other institutions associated with the study. The information can be obtained either by verbal interview and/or questionnaire.

The audit team will interview the investigator and all key personnel to assess their knowledge of the study, the informed consent process, and human subject protections for this study.

The audit team will also have the authority to directly observe the consent process.

On completion of the audit, a full written report will be prepared and presented to the IRB outlining audit findings and recommended actions, if any.

SECTION 19.6 FOR-CAUSE AUDIT

A for-cause audit, while having a general compliance component, is in response to specific complaints or concerns. It must be done in a careful and thorough manner. It must also be done in a timely manner since the study in question may already have been suspended.

SECTION 19.6.1 APPOINTMENT OF AUDITORS

A for cause audit team will be selected in the same manner as for a random audit. Particular attention will be paid to ensuring the independence and expertise of the team members.

The members of the audit team will be selected by the IRB.

SECTION 19.6.2 PROCEDURE

Prior to beginning a for-cause audit, the audit team will meet to review the allegations or concerns that have been presented to the IRB. In addition to the elements of a full random audit, the audit team will develop a plan for evaluating and addressing the specific concerns.

The investigator will be contacted and informed of the pending audit. The investigator, in addition to the documentation listed in Section 4, will provide the team with a list of all subjects enrolled in the study.

The investigator may also be requested to provide answers to specific questions generated be the audit team, and may also provide such additional information the investigator believes relevant.

In addition to interviews and document examination to answer the concerns presented to the board, the audit team will carry out the other elements listed under a full random audit.

If the team discovers a violation that may affect subject safety, the team leader will have the authority to take emergency action to ensure subject safety, to include the authority to suspend the study pending IRB review and action. It this occurs, this should be reported to the IRB chair immediately, and to the IRB at the next scheduled meeting. The IRB chair can uphold or reverse the suspension, but the action must be reported at the next scheduled IRB meeting. Only the IRB will have the authority to take final action.

SECTION 19.7 REPORTING THE FINDINGS OF THE AUDIT

The audit team will provide a written report to the IRB with a copy to the investigator. The scope and detail of the report will be consistent with the level of review. It will include the complete audit form and, if appropriate, an additional summary of findings, along with recommendations. Recommendations may be for no changes, administrative changes, or substantive changes. If serious violations are found, the audit team can make other recommendations up to and including closing the study or referring the investigator to the academic misconduct committee.

If, in the course the audit, violations are found that may place the subjects at risk, the auditor or audit team will have the authority to order the immediate suspension of the study. The team will report the suspension to the Chair of the IRB within 24 hours; the chair can either rescind or uphold the suspension pending review by the entire IRB.

The investigator may present a written response to the IRB for review. The IRB will review the audit findings and recommendations as well as the investigator's response for a final determination. The findings cannot be reversed by any institutional official but can be reassessed by the IRB if new information is provided.

SECTION 19.8 RESPONDING TO AUDITS

The IRB Board will review all audit findings. Findings may be accepted, remanded back to the audit team for changes, or rejected. If exceptions are found, the board will be responsible for making final findings. It the findings are adverse, the Investigator will be given an opportunity to present a response to the board. If the board then affirms its final findings, there is no further appeal.

The IRB may also make recommendations to the Investigator regarding suggested improvements regardless of formal findings. The board will distinguish between formal findings, which are mandatory, and general, non-binding recommendations for improvement.