IRB MEMBER HANDBOOK

Institutional Review Board
University of Tennessee Health Science Center
910 Madison Avenue, Suite 600
Memphis, TN 38163
901-448-4824
irb@uthsc.edu

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Introduction

This handbook is designed to help you become familiar with the terms, procedures, and federal regulations for the protection of human research subjects. New UTHSC IRB members always have many questions regarding IRB practices and the use of iMedRIS, our electronic research submission software. We encourage you to let staff know about your training needs as a new Board member.

Over time, you will be exposed to a multitude of differing research studies--some with unique sets of circumstances that require use of additional federal guidelines. At IRB meetings you will learn about regulations that pertain to vulnerable subjects such as children, pregnant women and fetuses, and prisoners. There will also be IRB reviews for studies involving humanitarian use devices; emergency use of drugs, biologics, and devices; compassionate / treatment use of drugs, biologics, and devices; and emergency medicine research where informed consent is waived.

As an IRB member you are not required to become an expert in these federal regulations. The IRB Chair and administrative staff will be able to assist you with questions that you may have as a reviewer for a study that involves the situations described in Part 2 of this IRB member handbook. Just remember that **your expertise and unique perspective as a reviewer is valued** even if you do not have experience in any of the special circumstances described.

Chapter 1: The IRB Member and the Culture of the Institutional Review Board

This chapter provides information regarding basic responsibilities as a board member. It is designed to answer common questions regarding membership.

Welcome!

The administrative staff at the University of Tennessee Health Science Center (UTHSC) Institutional Review Board (IRB) welcomes you as an IRB member. As you learn your responsibilities of participation there are many resources available to you and please contact any staff member at the Institutional Review Board if you have any questions. This handbook provides the basic information that you will need to get started.

As a new member, your first study review assignments will be relatively simple ones. As you become more experienced, the difficultly level of your reviews will increase. Ultimately you will develop a sufficient understanding and working knowledge of human subjects research and regulatory compliance.

Training

Newly appointed members complete one-on-one training with the Director or Associate Director so that he/she can familiarize himself/herself with the IRB process, policies and procedures, and IRB electronic system, iMedRIS.

Human subjects protection training via Collaborative IRB Training Initiative (CITI) is required for those who are involved with research at UTHSC and its affiliate institutions as well as Board members and Department Chairs. UTHSC Administration has determined these individuals should take Basic Human Subject Protections + Good Clinical Practice (Basic HSP + GCP) combination course (22 modules) **or** Human Subjects Training Basic Biomedical (Biomed) course (18 modules) plus GCP for Clinical Trials with Investigational Drugs and Medical Devices (US FDA Focus) course (14 modules). Follow the links below in order to obtain your *CITI* certificate, and let the IRB staff know when you have completed it. You should complete CITI training before your first meeting. Please note that if you have previously taken CITI training, you may take a shortened refresher course when your certificate expires every 3 years. You must pass the recertification test at 85% or higher, or you have to take the initial IRB member training course again.

Collaborative IRB Training Initiative (CITI) Program

- Available online at www.citiprogram.org
- Instructions are available on the IRB website at https://uthsc.edu/research/compliance/irb/training-and-education/irb-and-imedris-training.php
- This training must be renewed every 3 years.

IRB Insights are training opportunities that are provided periodically throughout the year for both researchers and board members. These training opportunities provide information about federal regulations, IRB policies and procedures, the IRB process, and iMedRIS.

During meetings of the full-convened IRB, the Chair will periodically present PowerPoint slides that include federal, state, and university regulations pertaining to the studies that are under review at that meeting. In addition, board members are provided information sheets that include the federal regulations when a study or project is being reviewed that includes a vulnerable population, humanitarian use device, compassionate/treatment use, emergency use, etc.

Confidentiality

During your association with the UTHSC IRB you will receive proprietary and confidential information. This information includes, but is not limited to, protocols and other information supplied by the UTHSC IRB regarding the use of human research subjects, drugs, biologics or devices, study results, and related materials, whether disclosed orally or in writing. It is essential that you honor the confidentiality of all sensitive information and use care in handling such privileged information so that it is not accidentally or intentionally disclosed.

All members must complete the IRB's *Confidentiality Acknowledgement* form within iMedRIS.

Resources

The UTHSC IRB website that contains many resources for the Researcher, Research Participants, and Board Members.

What does an IRB do?

The primary function of the IRB is to assist the principal investigator of the research study in the protection of the rights and welfare of human subjects. It is necessary for others who are independent of the research to share the responsibility for determining the standards for ethical conduct of research involving human subjects. The principal investigator over the research study, however, carries the primary responsibility for ensuring that the conduct of the research study measures up to standards established by the IRB.

How many IRBs are part of the UTHSC system?

The UTHSC IRB is comprised of 5 sections.

- Sections 1-4 of the IRB meet monthly in 910 Madison, Suite 502, Memphis, TN or Zoom on the first, second, third, and fourth Wednesdays of the month, respectively, at different times. These sections are for research studies that are conducted at UTHSC Memphis and its affiliate institutions. The meeting schedules are located on the IRB website at https://uthsc.edu/research/compliance/irb/researchers/meeting-schedule.php

What is the scope of the UTHSC IRB?

UTHSC established its Institutional Review Board in 1972. The IRB has oversight authority for all research with human subjects conducted by faculty, staff, fellows, residents, or students at UTHSC. The IRB in Memphis has responsibility for the review of research involving human subjects for Campbell Clinic, Le Bonheur Children's Hospital, Methodist Healthcare-Memphis Hospitals, Regional One Health, and physician practice groups such a UT Le Bonheur Pediatric Specialists, UT Regional One Health Physicians, and University Clinical Health. In addition, the UTHSC IRB has oversight authority for some human subjects research conducted by faculty, staff, students, residents, and fellows at Semmes Murphey.

Further, the UTHSC IRB reviews non-research requests for the use of drugs, biologics, or devices under the federal regulations pertaining to emergency use, compassionate use/treatment use, and humanitarian use devices (HUDs).

In addition, the IRB maintains a reliance agreement (also called a cooperative agreement, IRB authorization agreement, or memorandum of understanding) with the following organizations:

- St. Jude Children's Research Hospital
- National Cancer Institute CIRB program
- University of Memphis

Finally, the IRB at its discretion may oversee research activities conducted by non-UTHSC personnel who are not covered by any of the aforementioned agreements.

UTHSC faculty, staff, students, residents, or fellows conducting human subjects research at a Veterans Affairs facility, including the VA Medical Center at Memphis, or a Department of Defense (DoD) facility, should obtain approval from the appropriate VA or DoD IRB and do not need to undertake any interactions with the UTHSC IRB.

The IRB in Knoxville has the responsibility for the review of human subjects research at the Graduate School of Medicine in Knoxville and the UT Medical Center in Knoxville, an independent not-for-profit organization operated by University Health System, Inc.

The UTHSC IRB has the authority to approve, require modifications in, and disapprove research protocols based on the consideration of human subjects protection, including the authority to:

- Require progress reports from the investigators and oversee the conduct of the study,
- Investigate complaints or reports of noncompliance or protocol deviations,
- Suspend or terminate approval(s) or place restrictions on a study,
- Evaluate the risk/benefit status of studies,
- Ensure the adequacy of the informed consent process and informed consent documentation,
- Manage potential conflicts of interest in the research, and
- Ensure that the research has in place adequate mechanisms to protect human subjects, including the auditing of sites and monitoring of the informed consent process by using third party monitors.

Who is on the IRB?

- The Chair is a member of the IRB whose experience and expertise is documented in his/her CV. The Chair is appointed by the UTHSC Vice Chancellor for Research. The Chair serves a term of three years and may serve successive terms at the discretion of the Vice Chancellor for Research.
- The IRB Director holds a voting position on the UTHSC IRB. The director manages the daily operations and administrative activities of the IRB.
- The IRB Associate Director, the Senior Regulatory Specialist, Regulatory Specialists, IRB Administrators, IRB Reliance Managers, IRB Reliance Liaison, and the IRB Compliance Advisor are administrative staff members in the IRB and may hold a voting position on the Board.
- UTHSC IRB will include at least one member whose primary concerns are in the scientific area (examples: physicians, nurses, pharmacists, and dentists); at least one member whose primary concerns are in nonscientific areas (examples: lawyers, clergy, administrators, ethicists); and at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution (sometimes called a community member). Membership may include, but is not limited to: ethicists; members of the legal profession; clergy; members of the medical and other health care professions; other scientists or non-scientists to provide the necessary expertise to evaluate the research proposals and the informed consent process; lay persons representing the values and attitudes of the community from which research subjects are drawn; representatives of special populations, such as a prisoner representative; and

members representing research administration at Regional One Health, Le Bonheur Children's Hospital, and Methodist Healthcare—Methodist Hospitals.

Why is a community member an important part of the IRB?

The community member's responsibility on the Board is to provide a view of the research study as through the lens of the research subject. In addition, the community member may represent a socio-economic or ethnic group's voice to the IRB's decisions. Whether or not you are a community member, it is your duty to review a research study by:

- Viewing the study as if you were one of the participants,
- Ensuring that the informed consent form explains the research study in lay terms, and
- Determining whether the risks associated with the study are weighed and properly explained in the informed consent form.

What are my responsibilities?

- Your opinion is valued, therefore; express your ideas.
- Ask questions. If you do not understand a part of a research study, then it is likely a research subject will not understand. When in doubt, get clarification.
- Attend the majority of your board's meetings.
- Confirm or decline your board member attendance and reviewer availability through the electronic system, iMedRIS, three weeks before the meeting.
- Review your assigned study by the specified due date.
- Keep the proceedings of the IRB meeting confidential.
- Call the IRB staff and ask questions--they will be happy to help you!

Chapter 2: IRB 101

This chapter introduces the IRB policies and procedures and general information regarding regulatory compliance with federal, state, and local laws.

Any institution engaged in human subjects research that is supported or conducted by any department or agency of the federal government and which has adopted the Federal Policy for the Protection of Human Subjects [known as the Common Rule (45CFR46, Subpart A)] is required to establish a Federal Wide Assurance (FWA) with the Office for Human Research Protections of the Department of Health and Human Services (HHS). Under the terms of the Assurance, all of the institution's human subjects research activities, regardless of whether the research is subject to federal regulations, must be guided by the ethical principles in The Belmont Report and other appropriate ethical standards recognized by federal departments and agencies that have adopted the Common Rule.

DEFINING THE TERMS

Research

Research is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. The following activities are deemed not to be research:

(1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Human Subject
A human subject is a living individual about whom an investigator (whether professional or student) conducting research: (1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

45 CFR 46 Common Rule (Subpart A)
The Common Rule is a federal policy regarding Human Subjects Protection that applies to 17 Federal agencies and offices. It does not apply to federal agencies that have not signed the agreement (e.g., Department of Labor, etc.). The main elements of the Common Rule include:

- Requirements for assuring compliance by research institutions
- Requirements for researchers' obtaining and documenting informed consent;
- Requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping.

The Common Rule includes additional protections for certain vulnerable research subjects.
(1) Subpart B provides additional protections for pregnant women, in vitro fertilization, and fetuses.
(2) Subpart C contains additional protections for prisoners.
(3) Subpart D does the same for children.

Belmont Report
The Belmont Report summarizes the three basic ethical principles identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.
The basic ethical principles are:

- **Respect for Persons:** A principle stating that (1) individuals should be treated as autonomous agents, and (2) persons with diminished autonomy are entitled to protection.
- **Beneficence:** A principle that entails an obligation to protect persons from harm. The principle of beneficence can be expressed through two general rules: (1) Do not harm; and (2) Protect from harm by maximizing possible benefits and minimizing possible risks of harm.

- **Justice:** A principle requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics in the same way.

All human subjects research undertaken by the University of Tennessee Health Science Center that is conducted or supported by any federal agency which has adopted the Common Rule must comply with the terms of the Common Rule as well as any additional human subjects regulations and policies of the federal agency which conducts or supports the research, and any other applicable federal, state, local, or institutional laws, regulations, and policies.

For research that is conducted or supported by HHS, the institution must also comply with all subparts of the HHS regulations at 45 CFR 46, i.e., Subparts A, B, C, and D.

For research that is not conducted or supported by any federal agency that has adopted the Common Rule, the University is voluntarily committed by the terms of its Federal Wide Assurance to apply all aforementioned laws and regulations. The Common Rule includes the requirement that each institution to which the Rule applies establishes an Institutional Review Board (IRB) to oversee the application of relevant ethical principles and federal regulations in the conduct of human research.

A similar requirement for IRB review derives from regulations of the Food and Drug Administration (FDA). For all clinical investigations using investigational drug and devices regulated under certain sections of the Food, Drug, and Cosmetic Act, FDA regulations require IRB review and the informed consent of subjects.

Although FDA regulations for the protection of human subjects do not require institutions conducting FDA-regulated human research to have their own IRB, local IRB policy requires that any UTHSC personnel conducting FDA-regulated studies secure prior review and approval of the UTHSC IRB.

IRB's are expected to develop their own standard operating procedures (SOP's) which detail how regulatory policies will be followed. All IRB members should be familiar with the SOP's which can be found on the IRB's website located at
https://uthsc.edu/research/compliance/irb/researchers/standard-operating-procedures.php

Additional information can be found at the following sites:

- OHRP: Protection of Human Subjects (45 CFR 46)
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- FDA: Protection of Human Subjects (21 CFR 50)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

- FDA: Institutional Review Boards (21 CFR 56)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56
- FDA: Investigational New Drug Application (21 CFR 312)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312
- FDA: Investigational Device Exemptions (21 CFR 812)
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812

Chapter 3: Clinical Research Trials:

This chapter provides an overview of research and clinical trials.

Earlier in this handbook the terms "research" and "human subject" were defined. The majority of research that the IRB reviews falls under the category of human subject "clinical research". The UTHSC IRB oversees the regulatory compliance of behavioral/social research too, but most of the IRB full board reviews are for clinical trials.

DEFINING THE TERMS

Clinical research
Clinical research is the study of a drug, biologic, or device in human subjects with the intent to discover potential beneficial effects and/or determine its safety and efficacy. Clinical research is also called clinical study and clinical investigation.

Behavioral and Social Sciences Research
Behavioral research refers to the study of overt actions; underlying psychological processes such as cognition, emotion, temperament, and motivation; and biologically-related behavioral interactions. Social science research encompasses sociocultural, socioeconomic, and sociodemographic status; biologically-related social interactions; and the various levels of social context from small groups to complex cultural systems and societal influences.

Clinical trial
A clinical trial is a controlled study involving human subjects designed to contribute to generalizable knowledge about the safety and/or effectiveness of an intervention or treatment. A clinical trial is one type of clinical research that follows a pre-defined plan or protocol. By taking part in clinical trials, participants can not only play a more active role in their own health care, but they can also access new treatments and help others by contributing to medical research.

Clinical trials are sponsored by government agencies, private organizations, and individual researchers who are seeking ways to improve the health of people living with chronic and life-threatening illnesses. Sponsors include:

- government agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veteran's Affairs (VA)
- pharmaceutical, biotechnology, and medical devices companies

- individual researchers
- health care institutions such as academic medical centers and health maintenance organizations (HMOs)

Clinical trials take place in a variety of locations, including hospitals, universities, doctors' offices, or community health clinics.

What are clinical trial phases?

Clinical trials are conducted in a series of steps, called phases – each phase is designed to answer a separate research question.

- **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase 1 studies may sometimes be divided into 1a and 1b. Phase 1a may be performed in healthy volunteers and Phase 1b may be performed in patients with a disease or exposure to disease.

- **Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety. Phase II studies are sometimes divided into Phase IIa and Phase IIb. Phase IIa may be designed to assess dosing requirements (how much drug should be given). Phase IIb may be designed to study efficacy [how well the drug works at the prescribed dose(s)].

- **Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

- **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

How are participants enrolled in a clinical trial?

Research participants are recruited by a variety of methods. A principal investigator may ask his/her own patient population whether there is any interest in participation in a research study. Mailings, television advertisements, web flyers, emails, and radio announcements are all methods of study recruitment. Additionally, a principal investigator may send letters to colleagues asking them to refer patients for a study.

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. This website is a service of the U.S. National Institutes of Health and also is a method that can be used to recruit research subjects.

What is involved in the informed consent process?

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for under the HHS regulations at 45 CFR part 46. This requirement is founded on the principle of respect for persons, one of the three ethical principles governing human subjects research described in the Belmont Report. The principle of respect for persons requires that individuals be treated as autonomous agents and that the rights and welfare of persons with diminished autonomy be appropriately protected. The Belmont Report states that an autonomous agent is "an individual capable of deliberation about personal goals and of acting under the direction of such deliberation." Respect for persons requires that prospective research subjects "be given the opportunity to choose what shall or shall not happen to them" and thus necessitates adequate standards for informed consent.

Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. This key information should include:

- The purpose of the study
- The phase of the study, if applicable
- A description of the investigational drug or device, if applicable
- A brief description of the procedures including: use of placebo, blinding, randomization, a description of the study arms, length of study participation, total number of visits, and list of procedures that are being performed for research purposes only
- A list of the most common risks
- Benefits
- Alternatives
- A statement that participation is voluntary

The informed consent process involves three key features:

1. Disclosing to potential research subjects the information necessary to make an informed decision;
2. Facilitating the understanding of what has been disclosed; and
3. Promoting the voluntariness of the decision about whether or not to participate in the research.

The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

The Basic elements of informed consent are:

1. A statement that the study involves research; an explanation of the purposes of the research and the expected duration of the subject's participation; a description of the procedures to be followed; and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation will be provided and an explanation as to whether any medical treatments are available if injury occurs, and if so, what they consist of or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
9. For research studies that involve genetic analysis, a statement regarding the protections for genetic information provided by the Genetic Information Nondiscrimination Act; and
10. Any research that involves the collection of identifiable private information or identifiable biospecimens must include one of the following statements:
    a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

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

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
6. The approximate number of subjects involved in the study;
7. A statement that the subjects' biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subject, and if so, under what conditions; and
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of the specimen).

An IRB may require that additional information beyond the basic and additional elements be given to subjects during the informed consent process, when in the IRB's judgment the additional information would meaningfully add to the protection of the rights and welfare of the subjects.

Broad Consent:

Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted as an alternative to the informed consent requirements outlined above. If the subject or the legally authorized representative is asked to provide broad consent, the following should be provided to each subject or the subject's legally authorized representative:

1. Items 2, 3, 5, and 8 under the basic elements of consent listed above as well as items 7 and 9 from the additional elements above if applicable;
2. A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;
3. A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;
4. A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);
5. Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;
6. Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and
7. An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

As you read through the research study documents or listen to a principal investigator’s presentation at a board meeting, there may be terms that are unfamiliar to you. There is a working list of research terms in the Appendix of this handbook.

Chapter 4: Types of Reviews and the Full Board Meeting

This chapter defines the type of reviews that the IRB conducts, the pre-review process, explains what happens at the full board committee meeting, and explains your responsibilities before and during the meeting.

The IRB Chair or designee will determine whether submissions qualify for full board review, expedited review, or exempt status. Full board review will be required for all studies that involve more than minimal risk or do not otherwise qualify for expedited review or exempt status.

DEFINING THE TERMS

Minimal Risk
The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Not Human Subjects Research (NHSR)
Certain kinds of investigative activities are not human subjects research (NHSR) as defined in the federal regulations for the protection of human subjects. Under University of Tennessee Health Science Center (UTHSC) IRB policy, determination of if a study qualifies as NHSR must be made by a submission to the UTHSC IRB. There are research databases and repositories that have been de-identified. The UTHSC IRB has given NHSR status to the use of these specific databases and repositories.

Exempt Status
Under Federal regulations, certain categories of activity are considered research, but can be declared **exempt** from further review. At the University of Tennessee Health Science Center, this determination is made by the IRB, not the researcher. Some examples of exempt projects are:

- Anonymous surveys or interviews;
- Public observation of behaviors:
- Specific kinds of retrospective chart reviews.

Expedited Review
Research activities with human subjects and it involves only activities in one or more of the categories of expedited procedures.
Some examples of expedited projects are:

- Drawing small amounts of blood for research purposes;
- The use of non-invasive diagnostic procedures; and
- Prospective recording of data and collection of specimens.

Full Board Review
Full board review will be required of all new studies that involve more than minimal risk to human subjects or do not otherwise qualify for expedited or exempt review, as well as all continuations and revisions that do not qualify for expedited review.
Some examples of full board review are:

- Research that involves more than minimal risk;
- A research study that is complex in nature and involves a vulnerable population (children, pregnancy women or fetuses, or prisoners); and
- Research that involves the collection of sensitive information such as mental health diagnoses, HIV, child abuse, etc.

Pre-review recommendation:
The questions, comments, or items from an IRB member or IRB administrative staff member, which are sent to the principal investigator prior to the IRB committee meeting. These issues need corrective action or responses prior to the full board meeting.

Proviso:
A condition, precondition or stipulation. A principal investigator could receive these stipulations that must be met before approval.

What is the IRB process for reviewing a research study or clinical trial?

- A principal investigator submits a research study proposal using our electronic system called iMedRIS. As a new board member, you will have individualized iMedRIS training conducted by the IRB staff. See the iMedRIS chapter of this handbook that provides a link to a step-by-step guide to iMedRIS use.
- IRB administrative staff review the study submission to ensure that the major components of the submission are included, such as the application, study protocol, investigator's brochure, package inserts, questionnaires, and informed consent forms. Staff review the submission for regulatory compliance as well.
- A reviewer assignment is completed using the iMedRIS system.
- If you are the reviewer assigned to the study, you may or may not have expertise in the area that the research study encompasses. Don't worry, review the study using ***your skills and your expertise.***

- From your reviewer form in iMedRIS, you will read and critique the study application, the research protocol, informed consent form, and any other documents that are included with the submission. The study will be placed on the IRB committee agenda for committee review.
- Initially you will be assigned to a continuing review or a study revision. As you become more familiar with the review process, you may be asked to review a new study application.

Continuing review of previously approved research must be conducted at defined intervals appropriate to the degree of risk as initially determined by the IRB, but no less than annually. Continuing review cannot be performed under an expedited review procedure unless the original study was initially approved under expedited review criteria or the study satisfies other specific expedited review criteria (e.g., when no subjects have been enrolled and no new risks have been identified). Under the previous Common Rule, continuing review and approval is required for all studies reviewed by UTHSC IRB until a termination request has been granted. Under the revised Common Rule effective January 21, 2019, expedited studies do not require continuing review, and, if a DHHS-regulated project has progressed to the point that it involves only one or both of the following then the IRB will not require further review. However, the investigator still must submit a final Form 3: Continuing Review to the IRB as a notification of their study status:

1. Remaining study activities are limited to data analysis, including analysis of identifiable private information or identifiable biospecimens, or
2. Remaining study activities only involve accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

All FDA-regulated studies and expedited DHHS-regulated studies approved (or approved pending response to administrative provisos) prior to January 21, 2019 will still be required to submit a Form 3: Continuing Review for review and approval prior to the assigned expiration date until the study is closed with the UTHSC IRB.

- IRB review of proposed revisions involves the determination of whether the criteria for initial approval of research will still be satisfied if the revisions are implemented.
- A full board research initial submission is reviewed by several persons prior to approval: Two board members, an IRB staff member, and the entire Institutional Review Board committee.
- Continuing review of research and revisions of approved studies are reviewed by one board member, an IRB staff member, and the entire Institutional Review Board committee.

What are the important considerations when reviewing a new study application?

- IRBs must determine that all of the following requirements are satisfied in accordance with FDA (21 CFR 56.111) and HHS regulations (45 CFR 46.111):

- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall with the purview of its responsibility.
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

- You will have checklists within your reviewer form in iMedRIS that will guide you through review of the regulatory considerations for the study.
- In addition to those checklists, consider the following while completing your assessment. Make comments or ask questions if you have them.
  - What is the purpose of the study and does it make sense as it is written?
  - What are the subjects asked to do? Will they be answering questionnaires, taking a drug, having surgery that uses a device? Is this clearly explained in the study application?
  - Does the potential benefit of the intervention surpass the potential risks that are involved?
  - Would you participate in this research study? Would you want your family member to be a research subject in the study you are reviewing?
  - Are precautions taken to safeguard a subject from potential harm?
  - Are precautions taken to protect the privacy of a subject and to ensure the confidentiality of private information/specimens?
  - Are there vulnerable subjects involved such as pregnant women, children, or prisoners?

- Is information consistent across the consent form, application, and protocol?
- Is the consent form written in language that is easily understood?

What are the important considerations when reviewing a continuation of a research study?

- You will have checklists within your reviewer form in iMedRIS that will guide you through review of the regulatory considerations for approval of continuation of a study.
- You will be asked to report on the progress of the research at the committee meeting. The report should include the following:
  - a brief synopsis of the research;
  - the number of subjects accrued and whether the rate of subject enrollment is as expected;
  - a summary of any unanticipated problems and available information regarding adverse events (such a summary may be a simple statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure);
  - a summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known;
  - a summary of any complaints about the research from subjects or others since the last IRB review;
  - a summary of any recent literature that may be relevant to the research;
  - a summary of any amendments to the research since the last IRB review
  - any relevant multicenter trial reports;
  - any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research;
  - any changes in the investigator's situation or qualifications and any changes in institutional commitments;
  - a review of the protocol and current consent document(s) and whether any changes are needed; and
  - whether the research appears to continue to satisfy all criteria for approval under the regulations at 21 CFR 56.111 or 45 CFR 46.111 (and sub-parts B, C, and D, when applicable).

What are the important considerations when reviewing a revision to a study?

- You will have checklists within your reviewer form in iMedRIS that will guide you through review of the regulatory considerations for approval of the study revision.

- You will be asked to report on the revisions of the research at the committee meeting. The PI should have incorporated the proposed revisions into the application, protocol, consent form and project descriptors, as appropriate, in order to facilitate proper review.
  The report should include the following:
  - whether proposed revisions alter the acceptability of the risk-benefit ratio for the study;
  - whether the proposed revision will require other changes in procedures to assure that the rights and welfare of subjects remain adequately protected;
  - whether the proposed revision necessitates amendment of the informed consent disclosure; and
  - whether the proposed revision preserves the ability to select subjects equitably.

Here is a summary of the IRB full board review process for new study applications, study continuations, and study revisions:

- Two board members are assigned to review a new study: A primary and secondary reviewer are assigned to assess a new research study proposal.
- One reviewer is assigned to assess a study continuation and one reviewer is assigned to assess a study revision.
- The assignments are made 2.5 weeks prior to the board meeting.
- IRB members cannot participate in the review of a research study in which the member has a conflict of interest. (See below for more information in the Conflict of Interest section.)
- A reviewer has about a week to complete the study review.
- An IRB staff member is also assigned as the analyst and collates the comments of the reviewer(s) in addition to his/her comments for the study. The staff member sends the pre-review recommendations via iMedRIS to the investigator and/or study contacts listed in the study application.
- The principal investigator must respond to the recommendations using the PI Response Form in iMedRIS within 5 days prior to the meeting. If all recommendations cannot be addressed before the meeting, the PI Response Form must still be returned to the IRB via iMedRIS.
- The application is finalized on the agenda and becomes available to all board members, along with the PI Response Form and all supporting documentation a few days before the meeting.
- For a new full board study:
  - A synopsis of the study is presented by the principal investigator or a co/sub-investigator at the meeting of the full Board, and questions and comments are fielded from members of the Board.
  - Faculty advisors and study coordinators are welcome at the presentation so that proviso letters may be more easily answered with the knowledge of the Board's concerns and the discourse from the meeting.

    - Following the departure of the investigator, the primary and secondary reviewers must present their assessment of any significant issues and make their motion to the Board. There may be discussion among board members regarding the study.
- For continuations and revisions, the assigned reviewer summarizes the study and presents the information to the Board.
- After each presentation (new study, continuation, or revision), the primary reviewer will make one of the following motions and a second will be obtained from the secondary reviewer for new applications and second will be obtained from the floor for continuations and revisions:
    - Approval without provisos—there are no pending actions needed for approval.
    - Approval pending satisfaction of administrative provisos—some issues remain that can be resolved administratively without need for an additional full board review.
    - Deferral of approval pending satisfaction of conditions requiring further review by the full board—the study needs major revisions but may be acceptable if presented to the full board for an additional review.
    - Disapproval—the study is unacceptable for human subjects research because of research design, risks, etc.
- After a motion is made and seconded, the Chair will open the floor for discussion on the motion.
- Following the discussion, the IRB chair will call for a vote among members.
- The assigned IRB administrative staff member (analyst) sends a letter to the principal investigator and study contacts informing them of the outcome status of the full board review.

The order of the IRB meeting usually follows the following sequence.

1. Call for recusal (abstaining from participation if there is a conflict of interest regarding any of the studies to be reviewed during the board meeting).
2. Vote to approve the last meeting's minutes
3. New applications requiring full board review
4. Continuations of studies requiring full board review
5. Amendments / Revisions requiring full board review
6. Adverse Events / Unanticipated problems reported to the board
7. Protocol deviations
8. Miscellaneous / Other business, such as Audits

At times an educational component could be added to the meeting agenda in order to assist board members with the regulatory issues that may pertain to a particular study.

The IRB is required to apprise members of the actions that are conducted outside of the full Board meeting. Below are examples of items that may be listed below the agenda within

iMedRIS. These items are informational and are not discussed at the meeting unless a member of the Board has a question regarding the item.

- New Applications – Exempt
- New Applications – Expedited
- New Applications—Process Administratively
- Continuations—Process Administratively
- Revisions—Expedited
- Revisions—Process Administratively
- Events Reported as Unanticipated Problems
- Protocol Deviations
- Data Safety Monitoring Board (DSMB)/Annual Reports
- Documents from Reviewing IRB
- Recruitment Materials
- Study Closures

Quorum

The UTHSC IRB will conduct all business only when a quorum of members is present.

- The quorum is a simple majority of members of the specific section of the board that is meeting, but must include one non-scientific member.
- The IRB Director or designee will note in the minutes any loss of quorum.
- If quorum is lost, discussion and voting cannot occur.
- An abstention is when a member does not want to vote on a proposed item, for a reason other than a conflict of interest. An abstention is counted toward quorum.
- Please be on time so business can start on time.

Conflict of interest

1. An IRB member is considered to have a conflict of interest with respect to any item under review when any of the following conditions apply to the member or a family member [defined as a spouse (whether or not you commingle assets), parents, and children (both dependent and non-dependent, and including stepchildren and foster children)] thereof:
   a. The Board member or a family member has a *financial conflict of interest*.
   b. The Board member or a family member is a member of the research team engaged in the study under review.
   c. The Board member or a family member has direct supervisory responsibility in the employment setting for any of the investigators engaged in the study.
   d. The Board member or a family member is under the direct supervision in the employment setting of the principal investigator for the study.
   e. The Board member or a family member is the spouse of any of the investigators engaged in the study.
   f. The Board member or a family member serves as an officer of the agency, company or other entity sponsoring the research.

g. The Board member or a family member has some other interest that, in his or her individual judgment, constitutes a conflict of interest.
h. The Board member or a family member has some other interest that, in the judgment of the IRB chair, or the judgment of the convened Board as determined by a majority vote of those present, is determined to constitute a conflict of interest as defined in this policy.

The status of the Board member or a family member as a departmental colleague of any investigator engaged in a study under review is not considered, in and of itself, to constitute a conflict of interest.

2. In addressing *financial conflicts of interest*, the IRB follows the UTHSC General Policy: Conflicts of Interest & Commitment, effective 04/07/2022. Therefore, a conflict of interest exists when an individual (including the individual's spouse, whether or not they commingle assets, parents, and children, both dependent and non-dependent, and including stepchildren and foster children) has a significant financial interest that may affect the review of the research. A significant financial interest includes any of the following:

- The value of any remuneration received from a publicly traded entity in the previous 12 months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure which, when aggregated, exceeds $5,000; or
- The value of any remuneration received from a non-publicly traded entity in the 12 months preceding the disclosure which, when aggregated, exceeds $5,000, or when the individual holds any equity interest in that entity; or
- Intellectual property rights and interests (patents, trademarks, licensing agreements or copyrights) are held in the drug, device or other article being tested, and income related to such rights and interest has been received.

3. Federal regulations and IRB policy prohibit IRB members from participating in the review of any item with respect to which they have a conflict of interest, except to provide information as requested. IRB members are obligated to inform the IRB when they have a conflict of interest as defined above with respect to a specific study under review.

Chapter 5: iMedRIS

This chapter provides information and links to guides for using iMedRIS.

The UTHSC IRB utilizes iMedRIS [https://imedris.uthsc.edu] to process all research applications that are submitted to the IRB. It is a web-based system that enables online application submission, real-time submission tracking, review, post-approval compliance activities, and data management. The system also functions as a document repository, providing investigators with easy access to submission records and study documents.

Researchers and board members can use the system anywhere they have Internet access!

You will complete the following via iMedRIS:

- Mark meeting and reviewer availability at least 3 weeks before the meeting;
- Access the agenda;
- View submissions scheduled for review by the full convened IRB;
- Complete your reviewer assignments; and
- Access board members' reviews.

Email: When you are assigned a submission to review, you will receive an alert from iMedRIS to your UT email account or affiliated institution email account, if provided. If you regularly check another email, be sure to forward your UT email account to your other email address (excludes gmail and yahoo).

The iMedRIS Guide for Board Members provides navigational tips, instructions for completing meeting availability, accessing the meeting agenda, and steps to reviewing submissions as a primary/secondary reviewer.

Sample Reviewer Forms and other Guides and Tips are also available for Board members.

Note: You will need to enter your UT net ID and password to view these guides.

Chapter 6: IRB Administrative Staff

This chapter contains contact information of IRB staff members.

The IRB Administrative staff hopes that service as a board member will be a rewarding experience for you. At any time, please feel free to call us if you have any questions or if you need assistance with iMedRIS. We thank you for your willingness to serve, and we thank you for the time that you will devote to member duties.

Our Staff page includes names, position titles, phone numbers, and email addresses of the IRB staff.

Chapter 7: Waiver/Alteration of consent

This chapter contains information regarding waiving or altering the consent process.

The process of obtaining informed consent must normally involve an informed consent interview conducted in person. The UTHSC IRB may approve an alteration or waiver of informed consent under 45CFR46.116 provided that the IRB finds and documents the following conditions. Satisfaction of these conditions must be established by the principal investigator in the Form 1 application:

- The research involves no more than minimal risk to the subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The research could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The UTHSC IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the requirement for written documentation of consent is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

For example:

- The IRB may approve a waiver of consent when the PI requests to conduct a retrospective medical record review in order to collect data for research purposes.
- The IRB may approve an alteration of consent when subjects will be contacted by telephone to complete a questionnaire. The PI prepares a consent script to read to the subject prior to administration of the questionnaire.

For more information see the IRB Standard Operating Procedure for Informed Consent.

Chapter 8: Research When Children are Subjects

Children who are research subjects possess special vulnerabilities. This chapter contains information on how additional protections are afforded children as research subjects.

Research with children must satisfy the regulatory requirements of 45 CFR 46 Subpart D, "Additional Protections for Children Involved as Subjects in Research," and 21 CFR 50 Subpart D, "Additional Safeguards for Children in Clinical Investigations," as well as the general requirements of 45 CFR 46, Subpart A (the Common Rule). The UTHSC IRB shall determine that research with children satisfies the additional requirements outlined in Subpart D of the HHS and FDA regulations.

DEFINING THE TERMS

Assent means a child's affirmative agreement to participate in research. Mere failure to object, absent affirmative agreement, should not be construed as assent.

Children are persons who have not attained the legal age for consent to treatment or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

Permission means the agreement of parent(s) or legal guardian(s) to the participation of their child or ward in research.

Parent means a child's biological or adoptive parent.

Legal Guardian means an individual who is authorized by a court under applicable state or local law to consent on behalf of a child to general medical care. The term "legal guardian" as used here does not include non-custodial parents, grandparents, adult siblings, step-parents or other adult family members, unless such individuals are authorized by a court of law to make decisions about general medical care for the child.

Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

When reviewing clinical studies involving children that require full board review, UTHSC IRB will have a pediatrician and / or other voting member who has expertise, experience and training in

the care of children present when the study is discussed.

When reviewing clinical studies involving children, UTHSC IRB will only approve research studies falling into one of the following categories:

a. Research not involving greater than minimal risk to the research participant (45 CFR 46.404; 21 CFR 50.51).
b. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. Research in this category is approvable provided (a) the risk is justified by the anticipated benefit to the subject; and (b) the relationship of risk to benefit is at least as favorable as any available alternative approach (45 CFR 46.405; 21 CFR 50.52).
c. Research involving greater than minimal risks with no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; and (c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for the understanding or amelioration of the subject's disorder or condition (45 CFR 46.406; 21 CFR 50.53).
d. Research not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children (45 CFR 46.407; 21 CFR 50.54). When a research study is approvable only under this category, the IRB will request additional review by a panel of experts convened by the Secretary of HHS or the Commissioner of the FDA. Final approval will be contingent upon a finding by the expert panel that the study is approvable in accord with 45 CFR 46.407 or 21 CFR 50.54.
e. Children who are **Wards** of the State or any other agency, institution, or entity can be included in research approved under (2c) or (2d) only if (i) such research is related to their status as wards; or (ii) the research is conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards. If research is approved under this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.
f. The category under which the study is approved will be appropriately documented in the minutes of the IRB meeting.

In addition, the investigator must usually obtain both the written permission of the parent

or legal guardian, and the child's assent, before the child may participate in the study. A child's mere failure to object is not assent. Federal regulations do not require that assent be sought from children starting at a particular age, but specify that assent should be sought when, in the judgment of the IRB, the children are capable of providing their assent, taking into account the ages, maturity and psychological state of the children involved. UTHSC IRB policy is that assent must be obtained from all children ages 8 and older who are determined to be capable of providing assent.

Assent is a process initiated by a researcher to share information about a particular study with a child or minor adolescent subject. The basic value underlying this process is to acknowledge the minor as an individual deserving of respect. During the assent process, one or more of the following will be achieved: the minor can feel included in the process, or can feel at least partially informed, or can fully understand the purpose and requirements of the research. The extent of participation of the child in the process will be determined by the age and developmental status of the minor, relevant legal statutes, cultural contexts, type of research being done, local IRB policies, health status of the minor, and the potential for therapeutic benefit. The ultimate outcome of the process is agreement or disagreement by the minor to participate in the study.

The researcher may judge the clinical situation to be such that an assent process should not be initiated. In such situations the rationale for not initiating the assent process must be documented.

For more information regarding additional protections for children see the IRB policy Additional Protections for Children.

Chapter 9: Research Involving Pregnant Women, Fetuses, and Neonates

As research subjects, pregnant women, fetuses, and neonates possess special vulnerabilities. These vulnerabilities relate to an increased susceptibility to harm associated with research procedures, as well as impediments to provision of adequate informed consent (e.g., women in labor) or the absence of the ability to provide informed consent (fetuses and neonates). In this chapter you will learn about the additional protections that are afforded them as research subjects.

Research with pregnant women, fetuses and neonates must satisfy the regulatory requirements of 45 CFR 46, Subpart B, "Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research," as well as the general requirements of 45 CFR 46, Subpart A (the Common Rule). The UTHSC IRB shall determine that research with pregnant women, fetuses, and neonates is conducted in accord with 45 CFR 46, Subpart B. Finally, if a neonate is viable, then it may be included in research only to the extent permitted by the requirements of 45 CFR 46, Subpart D, "Additional Protections for Children Involved as Subjects in Research," and the requirements of the UTHSC IRB as outlined in IRB Standard Operating Procedure: Review of Research – Additional Protections for Children.

DEFINING THE TERMS

Dead Fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

Fetus means the product of conception from implantation until delivery.

Neonate means a newborn.

Nonviable neonate means a neonate after delivery that, although living, is not viable.

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

Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

1. Pregnant women or fetuses may be involved in research if all of the following conditions are met:
   a. Where scientifically appropriate, preclinical studies, including studies in pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
   b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
   c. Any risk is the least possible for achieving the objectives of the research;
   d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of 45 CFR 46;
   e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of 45 CFR 46, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
   f. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
   g. For children, as defined in 45 CFR 46.402(a), who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
   h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
   i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
   j. Individuals engaged in the research will have no part in determining the viability of a neonate.

2. Special conditions must also be satisfied for IRB approval of research involving certain categories of neonates:
   a. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:
      i. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

ii. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
iii. Individuals engaged in the research will have no part in determining the viability of a neonate.
iv. The requirements of paragraph (b) or (c) of this section have been met as applicable.

b. Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:
   i. The IRB determines that:
      (a) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
      (b) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
   ii. The legally effective informed consent of either parent/legal guardian of the neonate or, if neither parent/legal guardian is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent/legal guardian's legally authorized representative is obtained in accord with subpart A of 45 CFR 46, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

c. Nonviable neonates. After delivery, a nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:
   i. Vital functions of the neonate will not be artificially maintained;
   ii. The research will not terminate the heartbeat or respiration of the neonate;
   iii. There will be no added risk to the neonate resulting from the research;
   iv. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
   v. The legally effective informed consent of both parents/legal guardians of the neonate is obtained in accord with subpart A of 45 CFR 46, except that the waiver and alteration provisions of 45 CFR 46.116 do not apply. However, if either parent/legal guardian is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent/legal guardian of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents/legal guardians of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

d. Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of 45 CFR 46.

3. The IRB will approve research involving, after delivery, the placenta, the dead fetus, or fetal material in accord with the following requirements:
   a. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
   b. If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of 45 CFR 46 are applicable.

4. When research is not otherwise approvable under 45 CFR 46.204 or 45 CFR 205, but may present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, then the IRB will observe the following procedures:
   The Secretary of HHS will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 only if:
   a. The IRB will determine whether the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates. If the finding is positive, then the IRB will request that the Secretary of HHS convene an expert panel in accord with 45 CFR 46.207.
   b. The IRB will approve such research if the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
      i. That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or
      ii. The following:
         (a) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
         (b) The research will be conducted in accord with sound ethical principles; and
         (c) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of 45 CFR 46.

For more information regarding protections for pregnant women and fetuses see the IRB policy for Pregnant Women and Fetuses.

Chapter 10: Research Involving Prisoners

Incarceration places prisoners under constraints that may affect their ability to make truly voluntary and un-coerced decisions about whether or not to participate as subjects in research. Research involving prisoners constitutes a vulnerable population for which additional protections are warranted and is explain in this chapter.

The UTHSC IRB shall determine whether proposed studies with prisoners also satisfy the conditions enumerated at 45 CFR 46, Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects." These provisions of the federal regulations are intended to assure that prisoners provide voluntary consent to participation in research, that their confidentiality is rigorously protected, and that prisoners are not used as subjects in studies for which non-incarcerated subjects are suitable. They apply whether the research involves individuals who are prisoners at the time of enrollment in the research or who become prisoners after they become enrolled in the research. DHHS also requires that the IRB have among its members one or more individuals knowledgeable about and experienced in working with prisoners when research, involving prisoners, is to be reviewed. The current FDA regulations for the protection of human subjects, 21 CFR 50, 56, do not include any specific additional protections for research subjects who are prisoners. However, the FDA does consider prisoners to be a vulnerable subject population for which the IRB must include additional safeguards.

DEFINING THE TERMS

Prisoner means an individual involuntarily confined or detained in a penal institution, including persons:

- sentenced to such an institution under a criminal or civil statute;
- detained in other facilities (e.g. for the treatment of drug detoxification or alcoholism) by virtue of statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution, and
- individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c)).

Individuals are prisoners if they are in any kind of penal institution, such as prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

Examples of the regulatory definition of prisoner:

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or alternative to incarceration; however, individuals who

are receiving non-residential court-ordered substance abuse treatment and are residing in the community are not prisoners.

- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration; however, individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to non-penal institutions for treatment because their illness makes them a danger to themselves or others, are not prisoners.
- Parolees who are detained in a treatment center as a condition of parole are prisoners; however, persons living in the community and sentenced to community-supervised monitoring, including parolees, are not prisoners.
- Probationers and individuals wearing monitoring devices are generally not considered prisoners; however, situations of this kind frequently require an analysis of the particular circumstance of the planned subject population.

Permitted research involving prisoners must fall into one of the following categories:

a. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
   (Note that the definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk for other research, contained in 45 CFR 46, subpart A, 45 CFR 46.102(j))
b. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
c. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research; or
d. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.

During the review of any study involving the potential for enrollment of prisoners, in addition to normal review procedures, UTHSC IRB will consider the following:

IRB Membership: The composition of the IRB must satisfy the requirements of HHS regulations at 45 CFR 46.304 for IRB review of a protocol involving prisoners as subjects that is conducted or is supported by HHS, including the following:

- A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB;
- At least one IRB member must be a prisoner, or a prisoner representative with appropriate background, experience or working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner to serve in that capacity. The IRB will retain documentation of the current activities of the prisoner or prisoner representative serving on the IRB.
- Where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
- These requirements must be met during all types of protocol review including initial review, continuing review, review of protocol revisions and review of reports of unanticipated problems involving risks to subjects.
    - The IRB must notify OHRP of any change in the IRB roster occasioned by the addition of a prisoner or a prisoner representative as required by 45 CFR 46.108(a)(2).
    - Applicable State Laws: UTHSC IRB will consider applicable state laws in the review of these studies.

The institution engaged in the research must certify to the Secretary of HHS (through OHRP) that the proposed research falls within the categories of research permitted under 45 CFR 46.306(a)(2).

The IRB may utilize an expedited review procedure for new applications and revisions related to research involving prisoners, provided that:

- The decision to utilize expedited review is in accord with SOP: IRB Expedited Review;
- The prisoner representative determines that the research (or the revision to the research) involves no greater than minimal risk for the prison population; and
- The prisoner representative is assigned as an expedited reviewer on the application.

The IRB may utilize an expedited review procedure for continuation applications related to research involving prisoners, provided that:

- The research was initially approved as an expedited study;
- The decision to utilize expedited review is in accord with SOP: IRB Expedited Review;
- The prisoner representative determines that the research involves no greater than minimal risk for the prison population; and
- The prisoner representative is assigned as an expedited reviewer to the application.

Exception: The only time that a continuation for a full board study (that has been approved to include prisoners as subjects) can be reviewed using an expedited review procedure is when no subjects have been enrolled in the study.

For more information, see the IRB Policy for Additional Protections for Prisoners.

Chapter 11: Humanitarian Use Devices (HUD)

A humanitarian use device (HUD) is one that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 8,000 individuals in the United States in a calendar year. This chapter contains information on the IRB process of HUD approval.

The FDA authorizes the marketing of HUDs through the issuance of a Humanitarian Device Exemption (HDE). HDEs are intended to encourage the discovery and use of devices intended for the treatment or diagnosis of diseases or conditions that afflict small numbers of individuals who would be left without satisfactory treatment options in the absence of the availability of such devices. HDEs accomplish this goal by allowing device manufacturers to market a HUD in the absence of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. Rather, the manufacturer must only provide information indicating that the device will not expose patients to an unreasonable or significant risk, the probable benefit to health outweighs the risks associated with its use, and there is no comparable device available.

Although use of HUDs does not constitute research, FDA regulations governing their use require that the healthcare provider who will use a HUD obtain IRB approval before the HUD is used to treat or diagnose patients. The IRB is responsible for both initial and continuing review of the HUD use. In conducting its initial review, the IRB must determine that use of the HUD will be consistent with the approved labeling for the device. For continuing review, the IRB must follow the requirements at 21 CFR 56, but may use expedited review procedures unless it determines that full board review should be performed. The IRB may also use its discretion in determining whether to approve the use of an HUD for a given period of time, for a specified number of patients, or on a case-by-case basis. However, the HUD regulations require that the use of the HUD be reviewed by the IRB no less frequently than once a year. After approval by the IRB, the regulations require that the healthcare provider transmit to the IRB any medical device reports related to the occurrence of adverse events that must be submitted to the FDA in compliance with the reporting requirements of 21 CFR 803.

The HUD regulations do not address informed consent requirements for the use of a HUD. However, local IRB policy and applicable law require the informed consent of patients who will receive a HUD. The informed consent disclosure must indicate that the device is a HUD and that its effectiveness for the labeled indication has not been demonstrated. It must also contain a discussion of the potential benefits and risks of receiving the device and the availability of alternative treatments for the disease or condition.

Full Board review is required for any application to employ a humanitarian use device. Physicians must provide the following documents when submitting an application to use a HUD:

a. Form 1 study application;
b. FDA HDE letter authorizing marketing of the Humanitarian Use Device;
c. The HUD manufacturer's product label, clinical brochure and/or other pertinent information regarding operation of the device;
d. A summary of safety and probable benefits from the device manufacturer;
e. A written statement from the applicant specifying that use of the HUD will be limited to the clinical indications listed in the FDA-approved product labeling;
f. Information describing the applicant's clinical experience with the device, any training completed or required, and a list of physicians who will be using the device;
g. Prior annual reports of the manufacturer regarding the use of the device;
h. An explanation of the costs that patients will incur with use of the device;
i. Any advertisements or other descriptive materials that might be used in marketing the HUD.

The informed consent of the patient or the patient's legally authorized representative is required prior to the use of the HUD. The UTHSC IRB provides a consent form template on the IRB website.

For more information, see the UTHSC IRB Humanitarian Use Device policy.

Chapter 12: Emergency Use of a Drug, Biologic or Device:

This chapter addresses the procedures for use of a drug, biologic, or device in an emergency situation.

FDA recognizes that situations arise in which an investigational drug, biologic or device may be used on an emergency basis in a manner inconsistent with an approved protocol, in the absence of an approved protocol, or by a physician who is not an investigator on a clinical study. The FDA definition of the conditions under which emergency use is permissible involves two essential components: the presence of a life-threatening situation in which no standard acceptable treatment is available, and insufficient time to secure prior IRB approval. The emergency use provision is an exemption from prior IRB review and approval as specified at 21 CFR 56.104(c). While this exemption allows use of a test article in one subject without prospective IRB review, any subsequent use requires prospective review and approval.

Drug/biologic: The emergency use of an unapproved investigational drug or biologic normally requires an existing Investigational New Drug Application (IND). If medical circumstances require its use outside an approved protocol, the physician must contact the sponsor to determine if the drug or biologic can be made available for emergency use under the IND. The need for an investigational drug or biologic may also arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means to the FDA.

Device: The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but the device must be administered outside an approved IDE and/or protocol. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in a situation that satisfies the conditions for permissible emergency use. The physician must subsequently provide documentation to the FDA that an emergency actually existed.

When emergency care is initiated without IRB review or approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor can the outcome be included in any report of a research activity.

DEFINING THE TERMS

Emergency Use means the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval.

Life-Threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted, as well as diseases or conditions with potentially fatal outcomes. The criteria for a life-threatening disease or condition do not require the condition to be immediately life threatening or to immediately result in death. Rather the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely Debilitating means diseases or conditions that cause major irreversible morbidity including blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Test Article means an unapproved investigational drug, biologic or device for human use, including human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

1. Full Board approval is normally required for emergency use of a test article. If it is not feasible to convene a quorum before the treatment must be administered, and the treatment will be administered in a Methodist Healthcare facility or Regional One Health, then the emergency use may proceed without IRB approval only if the IRB Chairperson and the Medical Director of Medical Education and Research for Methodist Healthcare or the Chief Medical Officer, as well as Regional One Health's IRB representative concur in its use. If the treatment will be administered in any other institution, emergency use may proceed without IRB approval only if the IRB Chairperson concurs and the investigator obtains institutional clearance or approval according to the institution's policies and procedures. IRB approval using an expedited review procedure is not allowed.

2. IRB approval or concurrence for emergency use of a drug or biologic will occur only if all of the following conditions (specified at 21 CFR 56.102(d)) are satisfied:
   a. The patient has a life-threatening condition requiring treatment before review at a convened meeting of the IRB is feasible;
   b. There is no generally acceptable alternative treatment available; and
   c. There is not sufficient time to submit a protocol/amendment to the IRB for approval.

3. IRB approval or concurrence for emergency use of a medical device will occur only if all of the following conditions are satisfied:
   a. The patient is in a life-threatening condition that needs immediate treatment;
   b. No generally acceptable alternative for treating the patient is available; and
   c. Because of the immediate need to use the device, there is no time to use existing procedures to secure FDA approval for the use.

4. If the IRB approves or the Chairperson concurs with the emergency use, then:
   a. The IRB Chairperson will notify the physician seeking emergency use approval or concurrence.
   b. The IRB will use the date of concurrence to initiate tracking to ensure the investigator provides a report to the IRB within five days as required by 21 CFR 56.104(c) and again at one month after use of the test article.

5. For any emergency use, the investigator is required to obtain informed consent of the subject, the subject's legally authorized representative, or the parent/legal guardian unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23(a)):
   a. The subject is confronted by a life-threatening situation necessitating the use of the test article;
   b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject;
   c. Time is not sufficient to obtain consent from the subject's legally authorized representative or parent/legal guardian; and
   d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

6. If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions specified in (5) above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must submit the written documentation regarding the decision to proceed without informed consent to the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

7. The investigator must provide a report on the use of the test article and the outcome for the patient to the IRB within five days as required by 21 CFR 56.104(c) and again at one month after use of the test article. All correspondence and documentation relevant to the use of the test article must be submitted to the IRB as soon as possible, but no later than 5 days after notification of the use.

8. If the Sponsor requires a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104 (c) in order to approve shipment of the test article, the UTHSC IRB will provide such correspondence upon request.

9. After emergency use of a medical device, the investigator must notify the sponsor of the emergency use, if an IDE for the particular use exists. If an IDE does not exist, the investigator must notify the FDA of the emergency use and provide the FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results. If the emergency use involves a humanitarian use device, the report should be submitted to the HDE holder. Copies of the correspondence should be submitted to the IRB.

10. If the emergency use of the test article has occurred without approval of the full Board, the Chairperson will review the documentation submitted and report to the full IRB at the next convened meeting after the documentation is received.

11. UTHSC IRB will include in its correspondence to the investigator/physician a statement indicating that any subsequent use of the test article at the institution requires prospective IRB review and approval.

12. If the emergency use involves a test article utilized in an IRB-approved study, a copy of all correspondence and documentation concerning the emergency use will be kept in the IRB files for the study.

For more information, see the UTHSC IRB policy for Emergency Use of a Drug, Biologic or Device

Chapter 13: Compassionate/Treatment Use of a Drug, Biologic or Device:

This chapter addresses the procedures for use of a drug, biologic, or device for compassionate/treatment use.

Regulations of the FDA permit compassionate use/treatment use of unapproved drugs, biologics and devices outside the context of clinical trials for single patients or small groups of patients.

The **treatment use provisions of the drug and biologic regulations** allow access to an unapproved drug or biologic during its clinical investigation or prior to final action on the marketing application for patients who would meet the inclusion criteria for a clinical trial, but are not otherwise able to participate in a study. The patient(s) must have a serious or life-threatening disease or condition for which there is no satisfactory alternative treatment. The sponsor must be actively pursuing marketing approval. The treatment use may only occur after the FDA has approved a treatment Investigational New Drug Application (IND) from the sponsor of the investigational drug or biologic. Treatment use of an unapproved drug or biologic requires approval of the full Board and the informed consent of patients, as well as clearance from the institution in which the use will occur.

The **treatment use provision of the medical device regulations** allow access to an unapproved medical device during its clinical investigation or prior to final action on the marketing application for patients who would meet the inclusion criteria for a clinical trial, but are not otherwise able to participate in a study. The patient(s) must have a serious or life-threatening disease or condition for which there is no satisfactory alternative treatment. In the case of serious disease, an unapproved medical device can be made available for treatment use after all clinical trials have been completed. In the case of an immediately life-threatening disease, an unapproved medical device can be made available prior to the completion of all clinical trials. The sponsor must be actively pursuing marketing approval. The treatment use may only occur after the FDA has approved a treatment IDE application from the sponsor of the investigational device. Treatment use of an unapproved medical device requires approval of the full Board and the informed consent of patients, as well as clearance from the institution in which the use will occur.

The **compassionate use provisions of the medical device regulations** allow access to an unapproved medical device that is currently undergoing clinical investigation for patients who do NOT meet the inclusion criteria for the study. The device may be used in a single patient or in a small group of patients. The patient(s) must have a serious disease or condition for which there is no satisfactory alternative treatment. Prior FDA approval is needed before compassionate use occurs. The sponsor must submit an IDE supplement requesting approval for a protocol deviation in order to treat the patient(s). The physician should not treat the patient(s) until the FDA approves use of the device under the proposed circumstances. Compassionate use of an unapproved medical device requires the concurrence of the IRB chairperson and the informed consent of patients, as well as clearance from the institution in which the use will occur.

For more information, see the UTHSC IRB policy for Compassionate/Treatment Use of a Drug, Biologic or Device.

Chapter 14: Waiver of Consent for Emergency Medicine Research

This chapter contains information regarding the regulations to permit a limited class of research in emergency settings without consent.

The FDA regulation (21 CFR 50.24) provides a narrow exception to the requirement for informed consent from each human subject 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 representative or parent/legal guardian available prior to the time when the research interventions must be initiated. The intent of the new regulation 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 conduct of these studies.

FDA recognizes that persons with life-threatening conditions who can neither give informed consent nor refuse enrollment are a vulnerable population. FDA recognizes that the lack of autonomy and inability of subjects to give informed consent requires additional protective procedures in the review, approval, and operation of this research. The exception from the informed consent requirement permitted by the rule is conditional upon documented findings by an institutional review board (IRB). The required findings by the IRB are delineated in the procedures section below.

The provisions at 21 CFR 50.24 for the conduct of emergency medicine research with a waiver of informed consent are distinct from the waiver of informed consent for single patients or subjects as permitted under FDA regulations. The latter regulations apply to situations in which there are a need to use a test article to preserve the life of the patient or subject and it is not possible to secure the consent of the patient or subject prior to its use. Conditions for waiver of consent for emergency use are formulated at 21 CFR 50.23.

1. The IRB may approve, both initially and at the time of continuing review, an investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:
   a. 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.

b. 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 under investigation must be administered before consent from the subjects' legally authorized representative or parent/legal guardian is feasible; and
    iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
c. Participation in the research holds out the prospect of direct benefit to the subjects because:
    i. Subjects are facing a life-threatening situation that necessitates intervention;
    ii. 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
    iii. Risks associated with the investigation 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.
d. The clinical investigation could not practicably be carried out without the waiver.
e. The proposed investigational plan 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 or parent/legal guardian for each subject within that window of time and, if feasible, to asking the legally authorized representative or parent/legal guardian contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives or parents/legal guardians and make this information available to the IRB at the time of continuing review.
f. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representative or parent/legal guardian 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 clinical investigation consistent with paragraph (1)(g)(v) of this section.
g. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
    ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
v. If obtaining informed consent is not feasible and a legally authorized representative or parent/legal guardian 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 or parent/legal guardian, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

2. The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative or parent/legal guardian of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject or parent/legal guardian, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative, parent/legal guardian, or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative, parent/legal guardian, or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative, parent/legal guardian, or family member, if feasible.

For more information, see the UTHSC IRB policy for Waiver of Consent for Emergency Medicine Research.

APPENDIX

DEFINING THE TERMS

Adverse Event (AE): Any unanticipated problem involving risks to human research participants. An undesirable and unintended, although not necessarily unexpected, result arising during the course of a research protocol.

Adverse Event Reports: Investigator reports of all serious and adverse events, injury, and deaths given to the sponsor, the IRB, and the FDA.

Arm: A group or subgroup of participants in a clinical trial who receive specific interventions or no intervention, according to the study protocol. This is decided before the trial begins. The experimental arm is the group of participants that receives the intervention that is the focus of the study.

Assent: Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research.

Benefit: A research benefit is considered to be something of health-related, psychological, or other value to an individual research participant, or something that will contribute to the acquisition of generalizable knowledge. Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

Between Subjects Design: A research design in which there are separate groups of people being compared (smoker vs. nonsmoker).

Biologic: A biological product (as a globulin, serum, vaccine, antitoxin, or antigen) used in the prevention or treatment of disease.

Case-control Design: A study that compares two groups of people--those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the disease or condition. For example, one group may have been exposed to a particular substance that the other was not. Also called **Retrospective Design**.

Case Report Form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

Certificate of Confidentiality (CoC): A Certificate of Confidentiality is a declaration of protection that is issued by the Department of Health and Human Services. It prevents the compelled release of identifiable information about research subjects in any legal proceeding. A COC is often obtained when subject-sensitive information may be collected. Examples of sensitive information are drug and/or alcohol abuse, sexual or spousal abuse and HIV status.

Clinical Research Associate (CRA): An individual who represents the sponsor and who is responsible for the accuracy and management of data and overall supervision of day-to-day activities of the study. Also called a **Monitor**.

Code of Federal Regulations (CFR): A compendium of rules issued by federal agencies on a multiplicity of topics.

Coercion: The act of threatening, forcing, or pressuring an individual to consent to participate in research or to stay in research.

Cognitive Impairment: Some disorder that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished.

Cohort: A group of subjects initially identified as having one or more characteristics in common who are followed over time.

Co-Investigator: An individual who assists the principal investigator in conducting a sponsored project. A co-investigator usually works under the supervision and direction of the principal investigator. In the execution of a project, the principal investigator generally devises the research and methodology for the project, while a co-investigator participates in the research and has less direct responsibility.

Comparator (Product): An entity (active treatment or placebo) to which the test article is being compared.

Compensation: Refers to payment that will be given to subjects who volunteer to participate in research studies.

Competence: The capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting or not acting on that information, and to make a choice.

Control Group: Subjects in an experiment who do not receive the experimental treatment and whose performance provides a baseline against which the effects of the treatment can be measured.

Co-Principal Investigator: An individual that shares the administrative, fiscal, and scientific conduct of the research project. Each person can be named in the proposal and on project documentation as a Co-PI, provided this role is accepted by the **Sponsor**.

Crossover Design: An experimental design in which one group of subjects is exposed to more than one condition or treatment in random order; sometimes called a **Repeated Measures Design**.

Cross-Sectional Design: A study design in which data are collected at one point in time; sometimes used to infer change over time when data are collected from different age or development groups.

Data: Information organized for analysis or used as the basis for decision-making.

Data Points: Any text or numbers generated during a study.

Data and Safety Monitoring Board (DSMB): An independent committee whose function it is to provide data and safety monitoring of a research study. The Data and Safety Monitoring Board looks for any information that might warrant modification or termination of the trial, or notification of subjects about new information that might affect their willingness to continue in the trial.

Declaration of Helsinki: Statement of ethical principles first published in 1964 by the World Medical Association to define the rules for therapeutic and non-therapeutic research. It has been widely adopted by medical associations worldwide and has been revised numerous times.

Dependent Variable: The variable that the researcher believes will be influenced by the **Independent Variable**.

Deductive Reasoning: The process of developing specific predictions from general populations.

De-identified Data:
Data that is void of any of the following personal identifiers according to **HIPAA** regulations:

1. Names.
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:

A. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people, or
B. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.

All elements of dates (except year) directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of

dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
Telephone numbers.
Facsimile numbers (Fax).
Electronic mail addresses (E-mail).
Social security numbers.
Medical record numbers.
Health plan beneficiary numbers.
Account numbers.
Certificate/license numbers.
Vehicle identifiers and serial numbers, including license plate numbers.
Device identifiers and serial numbers.
Web universal resource locators (URLs).
Internet protocol (IP) address numbers.
Biometric identifiers, including fingerprints and voiceprints.
Full-face photographic images and any comparable images.
Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis, cure, treatment or prevention of disease. A device does not achieve its intended purpose through chemical action in the body and is not dependent upon being metabolized to achieve its purpose.

Double-Blind Experiment: An experiment in which neither the subjects nor those who administer the treatment know who is in the experimental or control group. Also known as **Double Blind Masking.**

Efficacy: A product's ability to produce beneficial effects on the duration or course of a disease. Efficacy is measured by evaluating the clinical and statistical results of clinical tests.

Emancipated Minor: A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities.

Emergency Research: Research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent. There are specific regulations that address this type of research.

Emergency Use: Use of a test article (drug or device) on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain prospective IRB approval.

Equitable: Fair or just. Used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.

Exclusion Criteria: The factors (or reasons) that prevent a person from participating in a clinical study.

Exculpatory: Pertaining to that which relieves of a responsibility, obligation, or hardship; clearing from accusation or blame.

Expected Adverse Event: For approved and marketed drugs or devices, those adverse events described in the approved Package Insert (Label). For investigational new drugs or devices, those adverse events described in the FDA Investigator's Brochure. In clinical research studies, information on expected adverse events are summarized in the consent form.

Experimental Drug: A drug that is not FDA approved for use in humans, or as a treatment for a particular condition in humans.

Experimental Group: Subjects in the study who receive the intervention being studied. The subjects will have similar characteristics as the subjects in the control group except for the fact they will receive the intervention.

Factorial Design: An experimental design in which two or more independent variables are simultaneously manipulated, permitting a separate analysis of the main effects of the independent variables, plus the interaction effects of those variables.

Fetal Material: The placenta, amniotic fluid, fetal membranes, and umbilical cord.

Generalizability: The degree to which the research methods justify the inference that the findings are true for a broader group than study participants; in particular, the inference that the study findings can be generalized from the study population to the general population.

Genotype: The genetic constitution of an individual.

Good Clinical Practice (GCP): Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are

credible. The objective of the International Conference of Harmonisation GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

HIPAA: The Health Insurance Portability and Accountability Act (HIPAA) sometimes called the "Privacy Act" went into effect April 14, 2003. The major goal of this law is to generally prohibit health care providers such as health care practitioners, hospitals, nursing facilities and clinics from using or disclosing protected health information without written authorization from the individual, i.e. a HIPAA Authorization.

Historical Control: Control subjects (followed at some time in the past or for whom data are available through records) who are used for comparison with subjects being treated concurrently.

Inclusion Criteria: A list of criteria that must be met by all study participants; the criteria that establish whether a person is eligible to participate in a clinical trial.

Independent Variable: The variable that is believed to cause or influence the **Dependent Variable**; in experimental research, the manipulated variable.

Inductive Reasoning: The process of reasoning from specific observations to more general rules.

Informed Consent: The process of information exchange between researcher and participant prior to written consent to participate in human subjects research. The informed consent process includes recruitment information, written materials, verbal instructions, and a question and answer session about the research and its procedures. Participants are given the opportunity to choose research involvement based on information, comprehension, and willingness to volunteer. The informed consent process is also an ongoing process throughout the subject's study participation.

Intervention: A process or action that is the focus of a clinical study. This can include giving participants drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include noninvasive approaches such education. Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Investigational New Drug: A drug or biological product that is used in a clinical trial but has not been approved by the FDA (the drug is either not available for a doctor to prescribe, or is available, but not approved by the FDA for the use being studied).

Investigational Device Exemption (IDE): The petition through which a study **Sponsor** requests an exemption from the Food, Drug, and Cosmetic Act to study investigational medical devices in humans and transport them across state lines.

Investigational New Drug Application (IND): The petition through which a study **Sponsor** requests an exemption from the Food, Drug, and Cosmetic Act to study investigational drugs in humans and transport them across state lines.

Investigator's Brochure: Relevant clinical and non-clinical data compiled on the investigational drug, biologic or device being studied.

Legally Authorized Representative: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective adult participant to his/her participation in the procedure(s) involved in the research. The State of Tennessee states that the LAR must be a competent adult who has exhibited special care and concern for the subject, who is familiar with the subject's personal values, who is reasonably available, and who is willing to serve. No person who is identified in a protective order or other court order that directs that person to avoid contact with the subject shall be eligible to serve as the subject's LAR. Identification of a LAR should normally be made using the following order of descending preference: conservator; guardian; attorney-in-fact; subject's spouse, unless legally separated; the subject's adult child; the subject's parent; the subject's adult sibling or any other adult relative of the subject; or any other adult who is familiar with the patient's personal values, who is reasonably available, and who is willing to serve. The term "family member" means any of the following legally competent persons who are not the legally authorized representative of the subject: spouse; parents; children (including adopted children); brothers; sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

Longitudinal Study: A study conducted over a long period of time.

MedWatch Program: An FDA program designed to monitor **Adverse Events** (AEs) from drugs marketed in the U.S. Through the MedWatch program, health professionals may report AEs voluntarily to the FDA. Drug manufacturers are required to report all AEs brought to their attention.

Meta-Analysis: A technique for quantitatively combining and thus integrating the results of multiple studies on a given topic.

Monitor: An individual employed by a pharmaceutical company, medical device manufacturer, or contract research organization that acts on behalf of the sponsor conducting a clinical trial.

Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore carried out by more than one investigator.

National Institutes of Health (NIH): Agency within DHHS that provides funding for research; conducts studies; and funds multi-site national studies.

National Research Act: Act created by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research in 1974 and mandated review of studies by institutional review boards and subject protection by informed consent.

New Drug Application (NDA): The compilation of all non-clinical, clinical, pharmacological, pharmacokinetic, and stability information required about a drug by the FDA in order to approve the drug for marketing in the U.S.

Nonsignificant Risk Device: An investigational medical device that does not present a significant risk. The determination that a device presents a nonsignificant risk is first made by the sponsor. If the IRB agrees with the sponsor's finding that a device presents nonsignificant risk, the device is considered a nonsignificant risk device.

Nuremberg Code: As a result of the medical experimentation conducted by Nazis during World War II, the U.S. Military Tribunal in Nuremberg in 1947 set forth a code of medical ethics for researchers conducting clinical trials. The code is designed to protect the safety and integrity of study participants.

Null hypothesis: A hypothesis stating there is no relationship between the variables under study.

Observational Research: Studies in which data are collected by observing and recording behaviors or activities relating to a phenomenon of interest.

Office for Human Research Protection (OHRP): This office interprets and oversees implementation of the regulations regarding the Protection of Human Participants in the Code of Federal Regulations (45 CFR 46). It is also responsible for providing guidance on ethical issues in biomedical and behavioral research. The OHRP has oversight and educational responsibilities wherever Department of Health and Human Services funds are used to conduct or support research involving human participants. It is located in the Office of the Secretary, Health, and Human Services.

Open-Label Study: A study in which all parties, (patient, physician, and study coordinator) are informed of the drug and dose being administered. In an open-label study, none of the participants are given **Placebos**. These are usually conducted with Phase I & II studies.

Off-Label: The unauthorized use of a drug for a purpose other than those purposes approved of by the FDA.

Outcome Measure: A planned measurement described in the **Protocol** that is used to determine the effect of interventions on participants in a clinical trial.

Parallel Design: Describes a clinical trial in which two or more groups of participants receive different interventions. For example, a two-arm parallel design involves two groups of participants. One group receives drug A, and the other group receives drug B. During the trial, participants in one group receive drug A "in parallel" to participants in the other group receiving drug B.

Pharmacodynamic (PD) Study: A study of a pharmacological or clinical effect of the medicine in individuals to describe the relation of the effect to dose or drug concentration.

Pharmacogenetics Study: A study of inherited genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.
Pharmacokinetics: The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

Pharmacology/Toxicology: The science of drugs and poisonous materials (respectively) and their effects on the body. Studies in these areas include: diet and nutrition; overdoses; and vitamin deficiencies.

Pilot Study: A pilot trial is used to obtain information, and work out the logistics and management, deemed necessary for further clinical trials.

Placebo: A substance that does not contain active ingredients and is made to be physically indistinguishable (that is, it looks and tastes identical) from the actual drug being studied.

Placebo Effect: A physical or emotional change, occurring after an inactive substance is taken or administered, that is not the result of any special property of the substance (placebo). The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

Power (statistical): The probability that you will observe a statistically significant treatment effect.

Primary Purpose: The one main reason for the clinical trial. Types of primary purposes include treatment, prevention, diagnostic, supportive care, screening, health services research, and basic science.

Principal Investigator (PI): The person responsible for the scientific and technical direction of the research project. The PI is also responsible for the proper conduct of the project including the submission of all required reports to the IRB, and FDA when applicable.

Protocol: A detailed plan that sets forth the objectives, study design, and methodology for a research project.

Protocol Amendment: A written description of a change(s) to or formal clarification of a **Protocol.**

Prospective Design: A study design that begins with an examination of presumed causes and then goes forward in time to observe presumed effects.

Qualitative Analysis: The organization and interpretation of nonnumeric data for the purpose of discovering important underlying dimensions and patterns of relationships.

Quantitative Analysis: The manipulation of numeric data through statistical procedures for the purpose of describing phenomena or assessing the magnitude and reliability of relationships among them.

Quasi-Experimental: An intervention study in which subjects are not randomly assigned to treatment conditions, but the researcher exercises certain controls to enhance the study's internal validity.

Randomization: The assignment of subjects to different treatment and sometimes non-treatment (**Placebo**) groups in a random manner.

Random Sample: A part (subset) of a larger population that is being studied where the subjects in the subset (sample) are selected at random. Each person in the larger population has an equal chance of being selected to be part to the sample.

Recruitment: Act of enrolling subjects with the proper **Inclusion Criteria**.

Reliability: The degree of consistency or dependability with which an instrument measures the attribute it is designed to measure.

Repeated Measures Design: An experimental design in which one group of subjects is exposed to more than one condition or treatment in random order; sometimes called a **Crossover Design.**

Research Hypothesis: The actual hypothesis a researcher wishes to test, stating the anticipated relationship between two or more variables.

Research Question: A statement of the specific query the researcher wants to answer to address a research problem.

Retrospective Design: A study design that begins with the manifestation of the **Dependent Variable** in the present and searches for the presumed cause occurring in the past.

Risk: A measure of (1) the probability of occurrence of harm to human health or (2) the severity of harm that may occur. Such a measure includes the judgment of the acceptability of risk. Assessment of safety involves judgment, and there are numerous perspectives (e.g., subjects, physicians, company, regulatory authorities) used for judging it.

Risk-Benefit Ratio: Risk to individual subject vs. potential benefits. Also called **Risk-Benefit Analysis**.

Sensitivity: The ability of screening instruments to correctly identify a case.

Serious Adverse Event: An **Adverse Event** that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.

Side Effects: Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects.

Single group design: Describes a research study in which all participants receive the same intervention. This is one type of study design with **Intervention**.

Significant Risk Device: An investigational medical device that (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is purported or represented to be of use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of

human health, and which presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Source Data: All information contained in original records and certified copies of results, observations or other facets required for the reconstruction and evaluation of the study that is contained in **Source Documents**.

Source Documents: The location where information is first recorded including original documents, data, and records.

Sponsor: Individual, company, institution, or organization taking responsibility for initiation, management, and financing of study.

Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the intervention is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Treatment or Standard of Care: The currently accepted treatment or intervention considered to be effective in the treatment of a specific disease or condition. This could be an accepted treatment nationwide, and/or the standard treatment provided by a particular physician, i.e. the **Principal Investigator**, or provided by a particular local clinic/practice.

Statistical Significance: Statistical evidence that a difference did not likely happen by chance (typically ninety-five percent likely). However, it does not refer to the size or the importance of the difference.

Sub-investigator: A member of the key study personnel that may help design and conduct investigation at a study site.

Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports **Adverse Events** and/or other trial-related data.

Test Article: Any drug, biological product for human use, medical device for human use, human food additive, color additive, or electronic product subject to FDA regulations under 42 USC 262, 263b-263N [21 CFR 50.3(j) and 56.102(e)].

Therapeutic Intent: The research investigator’s intent to provide some benefit to improving a subject’s condition.

Transferability: The extent to which findings can be transferred to other settings or groups.

Unexpected Adverse Event: An **Adverse Event** not described in the **Package Insert**, **Investigator's Brochure**, in published medical literature, in the protocol and/or in the informed consent document.

Validity: The degree to which an instrument measures what it is intended to measure.

Vulnerable Subjects: Group/individual who cannot give informed consent because of limited autonomy, for example, children and prisoners. Also refers to subjects who may be unduly influenced to participate (e.g., students and employees).

Waiver of Informed Consent: An action taken by the IRB permitting the investigator to pursue research involving human subjects without obtaining informed consent.