Methodist The Methodist Hospital Research Institute

POLICIES AND PROCEDURES FOR RESEARCH INVOLVING HUMAN SUBJECTS FOR

THE METHODIST HOSPITAL INSTITUTIONAL REVIEW BOARD NO. 1

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TABLE OF CONTENTS

APPENDICES

PREFACE

Pursuant to The United States Department of Health and Human Services ("DHHS") Office of Human Research Protections ("OHRP") regulations at 45 C.F.R. Part 46 (Subparts A-D), 21 C.F.R. Parts 50 & 56, The Methodist Hospital ("TMH") Federal-Wide Assurance [FWA#0000438] ("FWA" or "Assurance") (See terms of TMH Federal-Wide Assurance in Appendix B), and The Methodist Hospital Research Institute ("TMHRI") have established an Institutional Review Board ("IRB") to oversee human subject research studies to be conducted at TMHRI or any of The Methodist Hospital System hospitals (collectively "Methodist"). The IRB reports to the President & CEO of TMHRI through the TMHRI Office of Research Protection. The IRB has responsibility for approving, requiring modification to (to secure approval), or disapproving research involving human subjects. The IRB also has the authority to suspend or terminate such research for continued noncompliance with the DHHS Common Rule ("Common Rule"), FDA regulations, or its own findings, determinations, and initial and continuing review procedures. Other committees or officials of TMHRI may review and disapprove research approved by the IRB. However, no human subject research may be conducted at Methodist without the initial and continuing approval of an IRB that TMHRI specifically grants authority to regulate its human subject research ("Designated IRB"). A Designated IRB may be the TMHRI IRB or any other IRB that has explicit authority from TMHRI to regulate human subject research at TMH, TMHRI or its affiliated institutions and is also listed on TMH's FWA. Furthermore, no committee or official of Methodist may approve or authorize research to proceed involving human subjects that has not been reviewed and approved by a Designated IRB.

Chapter 1.
The Ethical Mandate to Protect Human Subjects

Human subject research at Methodist must be carried out in an ethical fashion. The following events are important milestones in the development of protections for human subjects in research.

a. The Nuremberg Code. The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related research experiments. The Nuremberg Military Tribunal developed ten principles, known as *The Nuremberg Code,* to judge the Nazi doctors. The significance of the Code is that it addressed the necessity to require the voluntary consent of the human subject and that any individual "who initiates, directs, or engages in the experiment" must bear personal responsibility for ensuring the quality of consent.

b. The Declaration of Helsinki. Similar principles have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, revised 1975, 1983, 1989, 1996, 2000),* which calls for prior approval and ongoing monitoring of research by independent ethical review committees.

c. The Belmont Report. Revelations about the 40-year United States Public Health Service Syphilis Study at Tuskegee and other ethically questionable research resulted in legislation in 1974 calling for regulations to protect human subjects and for a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the "Commission") to examine ethical issues related to human subject research.

The Commission's final and most influential report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,* describes three basic ethical principles that investigators must balance when conducting research with human subjects:

(i) **Respect For Persons** (operationalized by obtaining informed consent);
(ii) **Beneficence** (operationalized by weighing risks and benefits); and
(iii) **Justice** (operationalized by the fair selection of subjects).

The TMHRI IRB will adhere to the requirements of the Common Rule and the principles of the Belmont Report for all human subject research it reviews. A copy of The Belmont Report is available in Appendix C.

Chapter 2.
The Regulatory Mandate to Protect Human Subjects

TMHRI policies and Federal regulations require specific protections for human subjects.

a. **DHHS Regulations.**
DHHS regulations at 45 C.F.R. Part 46, Subpart A constitute the Federal Policy (Common Rule) for the Protection of Human Subjects. The DHHS regulations also include additional protections for pregnant women, fetuses and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D). All human subject research at Methodist must comply with all four Subparts of the DHHS regulations, as applicable. These regulations are enforced by OHRP. These regulations apply to all human subjects research conducted at Methodist. A copy of The Common Rule is available in Appendix D

b. **Food and Drug Administration ("FDA") Regulations.** The FDA has codified informed consent (21 C.F.R. Part 50), IRB (21 C.F.R. Part 56), and child protection (61 Fed. Reg. 20589 and 21 C.F.R. Part 50, Subpart D) regulations that are almost identical to the DHHS regulations. Additional FDA regulations relevant to the protection of human subjects address Investigational New Drug Applications ("IND") (21 C.F.R. Part 312), Biological Products (21 C.F.R. Part 600), and Investigational Device Exemptions ("IDE") (21 C.F.R. Part 812).

In general, FDA human subject regulations apply to clinical investigations and other research involving products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. IRB review and approval is required for clinical investigations and other research involving products regulated by FDA for human use, even where an IND or IDE is not required.

c. **The Assurance and IRB Registration Process.** Every institution that receives funds from DHHS and conducts human subject research must have an Assurance of protection for human subjects. 45 C.F.R. § 46.103.

Methodist currently conducts human subject research under a DHHS, OHRP-approved FWA. The TMHRI Office of Research Protection coordinates IRB registration and Assurance.

Chapter 3.
Defining Human Subject Research

a. Definition of Human Subject and Research. Federal regulations (45 C.F.R. § 46.102(d)) define research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."

Human subject research governed by Federal regulations falls into one of two categories: (i) minimal risk or (ii) greater than minimal risk.

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 45 C.F.R. § 46.102(i); 21 C.F.R. § 56.102(i).

Note that "minimal risk" is defined slightly differently when the research involves prisoners: In research involving prisoners as subjects, minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Federal regulations define **human subject** as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information." 45 C.F.R. § 46.102(f). **Private information** includes information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. **Identifiable** means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

While Federal regulations define a human subject as a "living individual," certain types of research on cadavers may also require oversight by the IRB. In most cases, an expedited review process would be acceptable.

b. Types of Human Subject Research. The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research.

1. *Biomedical Research.* Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, drug trials, medical device research, and cancer research are all examples of types of biomedical research.

2. *Social and Behavioral Research.* The goals of social and behavioral research are similar to those of clinical research -- to establish a body of knowledge and to evaluate interventions -but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs, and usually generates data by means of surveys, interviews, observations, studies of existing records, or experimental designs involving exposure to some type of stimulus or environmental intervention.

3. *Clinical Research.* Clinical research involves the evaluation of biomedical or behavioral interventions in a practice setting.

4. *Epidemiological Research.* Epidemiological research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy of interventions, or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs—such as those employed by the Centers for Disease Control and Prevention ("CDC")—whereas other epidemiological research may employ retrospective review of medical, public health, and/or other records. Because epidemiological research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may qualify for exemption or expedited review. In all cases, the IRB, not the individual investigator, will determine when IRB review of the activity is required.

5. *Repository Research.* Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB should review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols.

6. *Quality Assurance Activities.* Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities may constitute human subject research, and require IRB review, if they are designed or intended to contribute to generalizable knowledge. Quality assurance activities that are designed solely for internal program evaluation purposes with no application or generalization may not require IRB review. Where any disagreement arises about whether a quality assurance activity constitutes human subject research, the IRB, not the individual investigator, has final authority to determine when IRB review is required.

7 *Pilot Studies.* Pilot studies involving human subjects are considered human subject research and require IRB review.

Chapter 4.
Shared Responsibilities for Protecting Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust among the institution, investigators and their research staff, the subjects who enroll in research, and the IRB. A clear delineation of the responsibilities of each of these parties can help in assuring protections for the participants who volunteer for research as well as compliance with Federal regulations.

a. **The Institution.** It is the responsibility of the institution to assure federal agencies in writing that it will comply with regulations governing the protection of human subjects. As part of this Assurance, the institution must develop policies and procedures for conducting human subject research in a responsible and ethical fashion, including how research will be reviewed by the IRB, the reporting of unanticipated problems to the IRB and appropriate regulatory bodies, and other issues. The TMHRI Office of Research Protection maintains on file the current Methodist FWA that is applicable for all four Methodist hospitals and TMHRI.

The President & CEO of TMHRI serves as the Signatory Official of Methodist's Assurance and is ultimately responsible for overseeing the protection of human subjects within the institutions. The Institutional Signatory Official also maintains open channels of communication between the IRB, research investigators and staff, and administration, and provides the IRB with sufficient meeting space and staff to support its substantial review and record keeping responsibilities.

b. **The IRB.** The IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the Common Rule and FDA regulations, the IRB has responsibility for approving, requiring modification to (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

c. **The Principal Investigator.**

The Principal Investigator is that individual directly responsible for the human subject research described in the research protocol submitted to the IRB and must have the knowledge, skills, and experience necessary to qualify him or her for that role.

As the individual responsible for the implementation of research, the Principal Investigator has direct responsibility for ensuring the protection of every research subject in that study. This responsibility starts with protocol design, which must minimize risks to subjects in relation to research benefits. In addition, the Principal Investigator must ensure that all members of the research team are informed of and comply with the findings, determinations, and requirements of the IRB. The Principal Investigator must

also ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team actually obtain and document consent. Students (including graduate students) or trainees may not serve as the Principal Investigator at Methodist except under unusual circumstances, and they require specific approval by TMHRI Administration at the Vice President/Associate Director level or above, as well as by the IRB

Principal Investigators are responsible for ensuring that (i) all human subject research which they conduct at Methodist, or as employees or agents of TMHRI, has received prospective review and approval by the IRB designated by TMHRI or has been verified as exempt by the designated IRB; (ii) continuing review and approval of the research has been secured in a timely fashion; and (iii) the research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the the IRB. TMHRI Official Procedure RE-13 governs educational requirements and eligibility for research for Principal Investigators

NOTE: No changes in approved research (including all study procedures, subject recruitment materials, advertisements and informed consent documents and procedures) may be implemented without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects. No research may be continued beyond the IRB-designated approval period.

In addition, Principal Investigators must notify the IRB promptly of (i) any unanticipated problems or serious adverse events involving risks to subjects or others, and (ii) any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware.

d. **Other Members of the Research Team.** Every member of the research team is responsible for protecting human subjects. Co-investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, adhere to all protocol requirements, inform the Principal Investigator of all adverse reactions or unanticipated problems, ensure the adequacy of the informed consent process, and take whatever measures are necessary to ensure adequate protection for subjects. Researchers at every level are responsible for notifying the IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the designated IRB of which they become aware, whether or not they themselves are involved in the research.

e. **Research Subjects.** Subjects have responsibilities as well. They should be expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation. They should also be willing to comply with protocol requirements (unless they decide to discontinue participation) and inform the investigators of unanticipated problems

Chapter 5.
Institutional Review Board (IRB) Administration: IRB Roles and Authorities

a. **Human Subject Protections Under Federal Regulations.** Federal regulations at 45 C.F.R. Part 46 require that institutions engaging in human subject research funded by DHHS implement measures to protect human subjects. The regulations require that each institution conducting human subject research file a written Assurance of protection for human subjects and designate at least one IRB to review its human subject research.

The filing of Assurances and registration of the IRB are coordinated for the TMHRI IRB by the TMHRI Office of Research Protection, which has developed policies and procedures for the TMHRI IRB. These policies and procedures apply to all research involving human subjects, regardless of the source of funding, if any.

b. **Institutional Authority of the IRB.** The TMHRI President & CEO is responsible for all research activities conducted at Methodist or by TMHRI faculty.

The TMHRI Office of Research Protection may designate an IRB to review TMHRI human subject research. A Designated IRB may be operated by TMHRI or by any entity deemed appropriate by TMH and must be listed in the TMH Assurance.

c. **Purpose of the IRB.** The IRB has a primary responsibility to ensure that the rights and welfare of subjects are protected in human subject research. In doing so, the IRB must ensure that human subject research is conducted ethically, and in compliance with Federal regulations, the requirements of applicable Texas and local law, TMH's Assurance, and TMH's and TMHRI's policies and procedures. The TMHRI IRB fulfills these responsibilities by conducting prospective and continuing review of human subject research, including review of the protocol, the informed consent process, procedures used to enroll subjects, as well as any adverse events or unanticipated problems reported to the TMHRI IRB.

d. **Scope of the IRB's Authority.**

The IRB may take any action that it is legally permitted to take to protect the rights and welfare of human subjects in research conducted under its purview. The IRB has the authority to approve, require modifications in, or disapprove any human subject research.

The IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects as it determines necessary for the protection of those subjects, especially in instances of serious or continuing noncompliance. The IRB has the authority to observe, monitor, and/or audit human subject research to whatever extent it considers necessary to protect human subjects and assure compliance with applicable laws and regulations. In cases of serious or continuing noncompliance, the IRB may: (i) disqualify an investigator from conducting a particular research project or research altogether at the institution; (ii) require education and training in the ethics and regulation of human subject research; or

(iii) implement any other reasonable measures deemed appropriate to protect the rights and welfare of research subjects.

e. **Inter-institutional IRB Disagreements.** Should the TMHRI IRB and a collaborating institution's IRB disagree about the conditions necessary to approve a specific protocol, that disagreement must be resolved to the satisfaction of both IRBs before the protocol can be initiated or continued.

f. **Additional Institutional Review of IRB-Approved Research.** Although research approved by the IRB may be disapproved by other TMHRI committees or officials, no human subjects research may be conducted without the initial and continuing approval of the IRB. Thus, no Methodist committee or official may approve or authorize to proceed any human subject research that has not been reviewed and approved by the IRB and no Methodist committee or official may approve or authorize to proceed any human subject research which has been disapproved by the IRB. Additional institutional review of IRB-approved research must be coordinated with the TMHRI Office of Research Protection.

g. **Appeal of IRB Determinations.** No Methodist committee or official may set aside or overrule a determination by the IRB to disapprove or require modifications in Methodist's human subject research. The IRB will provide the investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and will give the investigator an opportunity to respond in person or in writing. The IRB will carefully and fairly evaluate the investigator's response in reaching its final determination. After the IRB has tabled a protocol three (3) consecutive times, that protocol will be deemed disapproved.

h. **Relationships and Responsibilities within the Institution.**

(i) As part of its obligation to report its findings and actions to the institution, the IRB will regularly forward copies of its meeting minutes to the TMHRI President & CEO.

(ii) Although normally reporting to the TMHRI Office of Research Protection, the IRB and/or its Chairperson may bring any matter directly to the attention of the President & CEO or the Vice President of TMHRI whenever a majority of the members and/or the Chairperson deems it to be warranted

(iii) The TMHRI Office of Research Protection may establish additional reporting relationships between the IRB and other officials or other committees as deemed appropriate

(iv) The IRB may require that proposed research be reviewed and approved by TMHRI's Radiation Safety Committee ("RSC") or Institutional Biosafety Committee ("IBC"), other TMHRI committees, or relevant committees of collaborating institutions.

(v) All persons conducting human subject research at must comply with all requirements of that IRB. Such persons must promptly provide the IRB with copies of any reports or correspondence to or from any regulatory agency (such as OHRP or FDA) that bear upon the protection of human subjects in research in which they

are involved.

i. Responsibilities to Regulatory Agencies. The IRB must comply with the requirements of all relevant regulatory agencies including OHRP and the FDA. Copies of any reports or correspondence to or from such agencies must be provided by the IRB to the TMHRI Office of Research Protection, which will determine whether any additional notifications are necessary.

j. Relationship of the IRB to Other Institutions. The IRB may be designated for review of research under another institution's Assurance only with the written agreement of TMHRI and in accordance with applicable requirements. Any such designation must be accompanied by a written agreement specifying the responsibilities of TMHRI and its IRB under the other institution's Assurance. The IRB has no authority over, or responsibility for, research conducted at other institutions in the absence of such a written agreement.

k Relationship of TMHRI IRB to IND/IDE Sponsors. Unless specifically required by an IND or IDE sponsor or by the IRB, no written notifications of IRB decisions will be provided to IND/IDE sponsors. The Principal Investigator usually serves as the communications link between the IRB and the sponsor. For FDA regulated test articles such linkage is agreed to by the sponsor and Principal Investigators when they sign the FDA Form 1572, Statement of Investigator.

l. Administrative Review of Human Protection Activities. The TMHRI Research Protection Officer is responsible for administrative oversight and review of Methodist's systemic protections for human subjects. This oversight and review may involve auditing of IRB files, subject records, or regulatory materials maintained by investigators and their staff and may be in conjunction with the THMRI Office of Compliance.

Chapter 6.
IRB Membership

a. Appointment of IRB Members. The President & CEO of TMHRI, under recommendation of the TMHRI Office of Research Protection, formally appoints members of the IRB. Members serve a one-year term, and are eligible for reappointment of additional one-year terms. Members vote to approve, require modifications to, disapprove, or defer research submitted to the IRB. Members are expected to attend IRB meetings on a regular basis, serve as primary or secondary reviewers for research within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings. Members are also expected to conduct expedited reviews on behalf of the IRB when so designated by the IRB Chairperson.

b. Appointment of IRB Chairperson. The President & CEO of TMHRI, under recommendation of the TMHRI Office of Research Protection, formally appoints a Chairperson of the IRB. The Chairperson serves a one-year term and is eligible for re-appointment. In addition to the responsibilities of IRB membership, the Chairperson has primary responsibility for conducting IRB meetings and directing IRB staff so that the IRB operates within all applicable regulatory requirements. The IRB Chairperson works with IRB members, institutional officials, and investigators to protect the rights and welfare of research subjects. As a fair and impartial committee head, the Chairperson functions as a role model for how IRB business should be conducted. The Chairperson also signs all official IRB correspondence.

c. Alternate IRB Members. The TMHRI Research Protection Officer also may appoint, one or more alternate members to replace regular IRB members who are, on occasion, unable to attend convened meetings of the IRB. Alternate members must be listed on the IRB's official membership roster, which must specify which member (or members) the alternate is qualified to replace. (Note: Although an alternate may be qualified to replace more than one regular member, only one such member may be represented by the alternate at any convened meeting.) Terms of appointment, length of service, and duties are exactly as for regular IRB members.

d. Non-Voting IRB Members. The President & CEO of TMHRI may appoint certain "non-voting" members to the IRB. Examples include TMHRI Research Compliance Office staff or Methodist attorneys who may be present at IRB meetings to answer questions or pose issues for discussion, but who may not vote and whose presence does not count towards quorum.

e. Consultants. An IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. Consultants may assist the IRB on either a regular or an as-needed basis.

f. IRB Membership Requirements. In compliance with Federal regulations at 45 C.F.R. § 46.107 and 21 C.F.R. §56.107, the IRB must satisfy the following requirements:

(i) The IRB will have at least five members;

(ii) IRB members will possess varying backgrounds to promote complete and adequate review of research activities commonly conducted;
(iii) IRB members will be sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects;
(iv) IRB members will include persons able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice;
(v) IRBs will consist of qualified persons of both sexes;
(vi) No IRB will consist entirely of members of one profession;
(vii) The IRB will include at least one member whose primary expertise is in a scientific area;
(viii) The IRB will have at least one member whose primary concern is in non-scientific areas;
(ix) The IRB will include at least one member who is not otherwise affiliated with Methodist and who is not part of the immediate family of a person who is affiliated with Methodist; and
(x) In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, terminally ill patients, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

g. Conflicts of Interest. No IRB member may participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members, including the IRB Chairperson, who have conflicting interests are required to disclose such interests and to absent themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences are recorded in the meeting's minutes. Since many IRB members also conduct research, it is their responsibility to adequately disclose any conflicting interests they may have.

h. Initial Training, Continuing Education, and Professional Development of IRB Members. Upon receiving an appointment to the IRB, members receivecomprehensive reference materials (including these operating procedures) necessary to review research from an ethical and regulatory perspective. All members are required to complete the TMHRI Human Subjects Protection Training program (e.g., CITI Course) and are encouraged to take a Good Clinical Practice training course. Members will periodically be provided with continuing education opportunities within Methodist or at neighboring institutions.

Chapter 7.
IRB Administrative Support

DHHS regulations at 45 C.F.R. § 46.103(b)(2) require that Methodist provide the TMHRI IRB with sufficient meeting space and staff to support the IRBs' review and record keeping responsibilities.

a. Resource Allocation. The TMHRI Research Protection Officer will recommend to the TMHRI President & CEO on an annual basis sufficient resources to support IRB review and record keeping responsibilities. The TMHRI President & CEO will include this information, as appropriate, in budget submissions.

b. Reporting Lines and Supervision. All IRB administrative staff ("IRB Professional Staff") report to and are supervised by the Director of the TMHRI Office of Research Protection.

c. Initial Training, Continuing Education, and Professional Development of IRB Professional Staff. Methodist is required under NIH policy to have a plan to provide education about human subject protections for IRB staff. All staff members are required to complete the CITI online training course and attend both internal and external conferences and seminars concerning human subjects protections (e.g. IRB 101). Staff members will periodically be provided with continuing education opportunities within Methodist or at neighboring institutions. IRB staff will periodically be provided with continuing education opportunities.

d. IRB Professional Staff Duties. IRB Professional Staff are responsible for the following IRB support functions, under the supervision of the TMHRI Director of the Office of Research Protections:

(i) Maintaining the official roster of IRB members;
(ii) Scheduling IRB meetings;
(iii) Distributing pre-meeting materials with sufficient time to allow IRB members an opportunity to review them in preparation for the meeting;
(iv) Compiling the minutes of IRB meetings in compliance with regulatory requirements.
(v) Promptly reporting changes in IRB membership to OHRP;
(vi) Maintaining all IRB documentation and records in accordance with regulatory requirements;
(vii) Assisting new IRB members with orientation procedures and in meeting required education standards;
(viii) Securely and properly archiving all IRB records;
(ix) Facilitating communication between investigators and the IRB;
(x) Tracking the progress of each research protocol submitted to the IRB;
(xi) Maintaining a computerized database for tracking purposes;
(xii) Serving as a resource for investigators on general regulatory information, and

providing guidance about forms and submission procedures;

(xiii) Maintaining training and reference materials related to human subject protection requirements;

(xiv) Maintaining and updating the IRB policies and procedures manual and IRB forms;

(xv) Drafting reports and correspondence to research investigators on behalf of the IRB or the IRB Chairperson regarding the status of the research, including conditions for initial or continuing approval of research and responses to reports of adverse events or unanticipated problems;

(xvi) Drafting reports and correspondence directed to research officials, federal officials, and others on behalf of the IRB or TMHRI IRB the Chairperson;

(xvii) Maintaining quality control of IRB support functions;

(xviii) Assisting in evaluation, audit, and monitoring of human subject research as directed by the IRB and the Research Compliance Office of TMHRI; and

(xix) Filing Assurance documents.

Chapter 8.
IRB Record Keeping & Required Documentation

Federal regulations require that Methodist implement written policies and procedures to govern the operations and direct the activities of the IRB. This IRB document satisfies that requirement.

IRB Professional Staff are responsible for developing and implementing procedures for efficient document flow and maintenance of all IRB records.

a. Record Retention. In accordance with Federal regulations at 45 C.F.R. § 46.115(b) and 21 C.F.R. §56.115(b), IRB records will be retained by Methodist for no less than three years, and research records will be retained by Methodist for no less than three years after the completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the FDA, OHRP, or other applicable agency.

b. Access to IRB Records. All IRB records will be kept secure in locking filing cabinets or in password protected secure systems. Inactive files will be secured in an off-premises, archival storage facility. Ordinarily, access to IRB records is limited to staff in the Office of Research Compliance, the IRB Chairperson, IRB members, Methodist's executives, as appropriate, IRB Professional Staff, Methodist's legal counsel, and officials of Federal and State regulatory agencies, including OHRP and FDA. Research investigators will be provided reasonable access to files related to their research. However, specific comments by IRB members, consultants, research subjects or others will only be provided in a redacted form so as to maintain confidentiality in the review and monitoring process. All other access to IRB records is limited to those who have legitimate need for them, as determined by the Director of the Office of Research Protection.

c. IRB Records. IRB records include files organized into the following categories:
(i) Written Operating Procedures;
(ii) IRB Membership Rosters;
(iii) Training Records;
(iv) IRB Correspondence (other than protocol-related);
(v) IRB Research Application (Protocol) Files;
(vi) Research (Protocol) Tracking System;
(vii) Documentation of Exemptions and Exceptions;
(viii) Documentation of Expedited Reviews;
(ix) Documentation of Convened IRB Meetings – Minutes;
(x) Documentation of Review by Another Institution's IRB; and
(xi) Adverse Event Reports.

d. IRB Membership Rosters. Any changes in IRB membership will be reported promptly to OHRP. All IRB membership rosters will include the following information:
(i) Names of IRB members;
(ii) Names of alternate members and the corresponding regular member(s) for whom

each alternate may serve;

(iii) Earned degrees and specialties of each member and alternate, if applicable, sufficient to describe each member's chief anticipated contribution to IRB deliberations;

(iv) The representative capacity of each member or alternate; and

(v) Any employment or other relationship with TMH (*e.g.*, full or part time employee, member of governing board, paid or unpaid consultant).

e. Education and Training Records. TMHRI will maintain accurate records listing research investigators, IRB members, and IRB staff who have fulfilled TMHRI's human subject protection training requirements.

f. IRB Correspondence. IRB Professional Staff will maintain accurate records of all correspondence to and from the IRB.

g. IRB Research Application (Protocol) Files. The IRB will maintain a separate file for each research application (protocol) that it receives for review. Each IRB research application (protocol) file will contain the following materials:

(i) The IRB Research Application (Protocol) Form;

(ii) Documentation of type of IRB review;

(iii) The IRB-approved informed consent document, with the beginning and ending dates of the current approval period clearly displayed on at least the first page;

(iv) Copies of all research proposals reviewed and scientific evaluations of the proposed research, if any;

(v) Applications for Federal support, if any;

(vi) Sponsor or cooperative group protocols and sample informed consent documents, if any;

(vii) Advertising or recruiting materials, if any;

(viii) Applications for protocol amendments or modifications;

(ix) Continuing review progress reports and related information;

(x) Reports of unanticipated problems involving risks to subjects or others;

(xi) Reports of injuries to subjects and adverse events occurring within Methodist (or involving employees or agents of Methodist) and reported to any regulatory agency;

(xii) Reports of external adverse events received from sponsors or cooperative groups;

(xiii) Data and Safety Monitoring Board ("DSMB") reports, if any;

(xiv) Results of any internal quality control and monitoring activities, if any;

(xv) All IRB correspondence to and from research investigators;

(xvi) All other IRB correspondence related to the research;

(xvii) Documentation of all IRB review and approval actions, including initial and continuing convened (full) IRB review;

(xviii) Documentation of project closeout; and

(xix) Documentation of statements of significant new findings provided to subjects.

h. IRB Database. TMHRI will maintain a research (protocol) tracking database. At a minimum, the database will include the following information:

(i) Title of the Research (Protocol);
(ii) Name of Principal Investigator;
(iii) Funding Source (if any);
(iv) Date of Initial Approval;
(v) Date of Most Recent Continuing Approval;
(vi) End of Current Approval Period;
(vii) Type of Review (Expedited or Convened Review); and
(viii) Current Status (Under Review, Approved, Suspended, Closed).

i. **Documentation of Exemptions.** The IRB Chairperson, or his or her designee, is responsible for reviewing and verifying, whether activities are exempt from the human subject regulations

Documentation of verified exemptions consists of the reviewer's written concurrence in the IRB Research Application File that the activity described in the investigator's Request for Exemption satisfies the conditions of the cited exemption category.

Categories of exempt research are stipulated in Federal regulations at 45 C.F.R. § 46.101(b)(1-6) as follows:

(i) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods;

(ii) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation;

(iii) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under 45 C.F.R. § 46.101 (b)(2), if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter;

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

(v) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or

otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(vi) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 C.F.R. 56.104(d)]

j. Documentation of Exemptions from IRB Review Requirements for Emergency Use of a Test Article. FDA regulations at 21 C.F.R. § 56.104(c) permit the emergency use of a test article without IRB review. Written documentation of the emergency use must be submitted to the IRB within 5 working days. Any subsequent use of the test article at Methodist requires IRB review. IRB Processional Staff are responsible for maintaining this documentation in IRB records.

k. Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article. FDA regulations at 21 C.F.R. § 50.23 permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the Principal Investigator and a physician not otherwise involved in the research certify in writing that (i) the subject is confronted with a life threatening situation necessitating the use of the test article; (ii) informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject; (iii) time is not sufficient to obtain consent from the subject's legally authorized representative; and (iv) there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the Principal Investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required above in advance of using the test article, the determinations of the Principal Investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

This written certification must be submitted to the IRB within 5 working days of the use of the test article. IRB Professional Staff are responsible for maintaining this documentation in IRB records. In addition, 21 C.F.R. § 50.23 (d) allows the President of the United States to waive informed consent for the administration of an investigational new drug to a member of the armed forces in connection with the individual's participation in a particular military operation.

l. Documentation of Exemption from IRB Review Requirements for Emergency Use of Investigational Drugs. Need for an investigational drug may arise in an emergency

situation that does not allow time for submission of an IND in accordance with 21 C.F.R. § 312.23 or § 312.34, as set forth in Paragraph B above. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of IND. Except in extraordinary circumstances, such authorization will be conditioned on the sponsor making an appropriate IND submission as soon as practicable after receiving the authorization.

Emergency use of an unabpproved or investigational drug in humans may be considered when a patient, or patients, meet the following criteria:

1. The patient has a life-threatening condition that needs immediate tratement;
2. No standard acceptable treatment is available; and
3. There is not sufficient time to obtain IRB approval.

Emergency use of drugs is exempted from prior IRB review and approval, but must be reported to the IRB within five (5) working days. Any subsequent use of the test drug at the institution is subject to IRB review.

Even for an emergency use, the investigator is required to obtain informed consent in accordance with 21 C.F.R. § 50.24 (See TMHRI Policy RE02).

m. Documentation of Expedited Reviews. Expedited IRB review procedures may be employed for (i) minor changes in previously approved research during the specified approval period, or (ii) initial or continuing review of research falling within specific categories published in the Federal Register. The IRB Chairperson or a qualified IRB member designated by the Chairperson conducts expedited reviews.

Documentation for expedited review and approval consists of the reviewer's written concurrence in the IRB Research Application File that the activity described in the Investigator's Request for Expedited Review satisfies the conditions (i) for a minor change, or (ii) of the cited or another expedited review category.

n. Convened IRB Meetings and Documentation—Minutes.

(1) Regular Meetings - The TMHRI IRB shall meet at least once each month. The IRB meeting schedule is posted on the TMHRI website.

(2) Emergency Meetings - The IRB Chairperson of his or her designee may call an emergency meeting of the IRB as necessary to address noncompliance or serious and/or unexpected events involving human.

(3) Minutes - IRB Professional Staff will compile the minutes of IRB meetings. The following specific information will be recorded in the meeting minutes:

(i) Attendance;
(ii) Quorum requirements;
(iii) Actions taken by the IRB on the initial or continuing review of research; review of protocol or informed consent modifications or amendments; unanticipated problems

involving risks to subjects or others; adverse event reports; reports from sponsors, cooperative groups, or DSMBs; reports of continuing noncompliance with the human subject regulations or IRB determinations; suspensions or terminations of research; and reports of injuries to subjects; and other actions The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB;

(iv) Votes on these actions, including the number of members voting for, against, and abstaining;

(v) The basis for requiring changes in or disapproving research;

(vi) Written summary of controverted issues and their resolution;

(vii) Required IRB findings and determinations; and

(viii) A list of research approved since the last meeting utilizing expedited review procedures.

o. **Attendance at IRB Meetings.** IRB minutes will list attendance as follows:

(i) Names of members present;

(ii) Names of absent members;

(iii) Names of alternates attending in lieu of specified (named) absent members Alternates may substitute for specific absent members only as designated on the official IRB membership roster;

(iv) Names of consultants present;

(v) Names of investigators present; and

(vi) Names of guests present.

p. **Quorum Requirements and Voting at IRB Meetings.** IRB minutes will include a statement of Quorum Requirements based on the following standards:

(i) A majority of the IRB members (or their designated alternate), including at least one member whose primary concerns are in nonscientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting;

(ii) Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference will be noted as such in the meeting minutes, which will also indicate that the members received all pertinent information prior to the meeting and were able to actively and equally participate in all discussions;

(iii) IRB minutes will include documentation of quorum and votes for each IRB action and determination by recording votes as follows: Total Number Voting; Number voting for; Number voting against; Number abstaining;

(iv) Members absenting themselves due to conflicting interests may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining); and

(v) No individual who is not listed on the official IRB membership roster and registered with OHRP may vote with the IRB.

q. **Actions Taken by the Convened IRB**. IRB minutes will include all actions taken by the convened IRB and the votes underlying those actions. These actions will also be

reported in writing to investigators in the form of a memorandum from the IRB which includes, at minimum, the following information (where appropriate): investigator name, title of study, IRB number, level of risk as determined by the IRB, approval date, continuing review interval, and any changes to the materials submitted in order to secure approval.

IRB actions for review of research include the following:

1. ***Approved with No Changes*** (or no additional changes). The research may proceed.

2. ***Action Deferred with Non-Substantive Changes***. These include *specifically stipulated changes* that are required, which can be reviewed by the IRB Chairperson or by a designated IRB member. Such stipulated changes must be clearly delineated by the IRB so the Principal Investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol is approved by the IRB Chairperson or designated reviewer.

3. ***Action Deferred with Substantive Changes required which will be reviewed by the convened IRB***. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research. Any requested changes, to which the Principal Investigator does not specifically agree will be treated as substantive, and response will be reviewed by the convened IRB.

4. ***Tabled.*** The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.

5. ***Disapproved.*** The IRB has determined that the research cannot be conducted at Methodist.

r. The Basis for Requiring Changes in or Disapproving Research.
The minutes of IRB meetings will include the basis for requiring changes in or disapproving research. This information will also be provided in writing to the Principal Investigator, who will be given an opportunity to respond in person or in writing.

s. Summary of Controverted Issues at Convened Meetings. The minutes of IRB meetings will include a summary of the discussion of all controverted issues and their resolution.

t. Required IRB Findings and Determinations. The following specific IRB findings and determinations will be documented in IRB meeting minutes, including protocol-specific information justifying each finding or determination:

(i) The level of risk of the research;

(ii) The approval period for the research, including identification of research that warrants review more often than annually;

(iii) Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research;

(iv) Justification for waiver or alteration of informed consent, addressing each of the 4 criteria at 45 C.F.R. § 46.116(d). Briefly, the criteria that the IRB must find and document are: (1) the research involves no more than minimal risk to subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation;

(v) Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 45 C.F.R. § 46.117(c);

(vi) Justification for approval of research involving pregnant women, human fetuses, and neonates, addressing each of the criteria specified under Subpart B of the DHHS human subject regulations;

(vii) Justification for approval of research involving prisoners, addressing each of the categories and criteria specified under Subpart C of the DHHS human subject regulations. The Research Protection Officer is responsible for providing certification of the IRB's findings to OHRP;

(viii) Justification for approval of research involving children, addressing each of the categories and criteria specified under Subpart D of the DHHS human subject regulations. The Research Protection Officer is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts;

(ix) Special protections warranted in specific research projects for groups of subjects who 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, regardless of source of support for the research; and

(x) Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under DHHS guidance provided pursuant to the special 45 C.F.R. § 46.101(i) DHHS waiver (guidance letter available at http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm) or the FDA exception at 21 C.F.R. § 50.24.

Chapter 9.
Types of IRB Review

All human subject research conducted at TMH or TMHRI or by their employees must be prospectively reviewed and approved by a TMHRI Designated IRB. No human subject research may be initiated or continued at or by Methodist or by Methodist's employees or agents without prospective approval of a Designated IRB. TMHRI IRB forms for submission are available at http://www.tmh.tmc.edu/tmhri/. The TMHRI IRB will engage in the following types of review.

a. **Review by the Convened IRB.** Federal regulations, the Federal Policy (Common Rule) for the Protection of Human Subjects, and FDA regulations require that the IRB conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review (see item "e" of this Chapter).

b. **Initial Review by the Convened IRB.** Prior to the convened meeting, IRB members will be provided detailed initial review materials describing the research in order to discuss the protocol adequately and determine the appropriate action during the convened review. These materials will include the IRB Research Application Form (Protocol), which includes information, as applicable,about subject recruitment and selection, the research plan, risks and benefits, privacy and confidentiality protections, safety monitoring, informed consent procedures, and protections for vulnerable subjects; the full industry protocol or investigator's project description; clinical investigator's brochure (if applicable); the proposed informed consent document; any recruitment materials (including advertisements to be seen or heard by potential subjects); and any other information relevant to the approval criteria described in the regulations. For DHHS multi-center trials, investigators must also submit DHHS-approved sample informed consent documents and the complete DHHS-approved protocol

c. **Continuing Review by the Convened IRB.** The IRB is required to conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. Continuing review will be conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review (see item "e" of this Chapter)

Prior to the convened meeting, IRB members will be provided with detailed continuing review materials sufficient to conduct substantive and meaningful reviews. These materials will include the currently approved informed consent document and the IRB Continuing Review Application Form, which includes a summary of the research, a status report on the progress of the research, number of subjects enrolled and withdrawn, problems and adverse events, relevant recent literature, and other relevant information.

d. **Use of Primary Reviewers with Convened IRB Reviews.** The IRB will utilize a primary reviewer system to assist in the initial and continuing review of research by the convened IRB.

The primary reviewer for initial review and the primary reviewer for continuing review are considered the lead reviewers for research proposals assigned to them. They are responsible for (i) being thoroughly versed in all details of the research; (ii) conducting an in-depth review of the research using the IRB Reviewer Forms; and (iii) leading the discussion of the research at the convened meeting. Prior to the convened meeting, the primary reviewer must be provided with all the documents listed in item "b" above. All other IRB members will receive the IRB Research (Protocol) Application form (which includes information about subject recruitment and selection, the research plan, risks and benefits, privacy and confidentiality protections, safety monitoring, informed consent procedures, and protections for vulnerable subjects), the proposed informed consent document, and any recruitment materials (including advertisements intended to be seen or heard by potential subjects)

The entire IRB file will be available to all IRB members, and all IRB members will be afforded full opportunity to discuss each research proposal during the convened meeting.

e. **Expedited Review of Research.** Federal regulations and the Federal Policy (Common Rule) permit the IRB to review research through an expedited procedure if:

(i) The research constitutes a minor change in previously approved research during the period for which approval is authorized; or
(ii) The research is not greater than minimal risk and falls within the categories on the November 9, 1998 DHHS-FDA list of research eligible for expedited IRB review.

Under an expedited review procedure, the IRB Chairperson or an experienced reviewer designated by the Chairperson may review and approve the research on behalf of the IRB. For continuing reviews approved by expedited review, the IRB Chairperson or experienced reviewer designated by the Chairperson should receive all of the documentation listed in item "c" above. When conducting an expedited review the Chairperson or his/her designee shall have all of the authority of the full IRB except that he/she may not disapprove research. **Disapproval may only be done by vote of the convened IRB.**

The IRB Chairperson will keep all IRB members advised of research that has been approved under expedited procedures by identifying the research in the agenda and minutes of the next IRB meeting.

Documentation for expedited reviews maintained in IRB records will include the category and circumstances that justify using expedited procedures.

f. **Expedited Review of Minor Changes in Previously Reviewed Research.** Principal Investigators must report to the IRB any proposed changes in IRB-approved research, including proposed changes in informed consent documents and subject recruitment materials. No changes may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects.

The IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period.

A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in (i) the level of risks to subjects; (ii) the research design or methodology; (iii) the number of subjects enrolled in the research; (iv) the qualifications of the research team; (v) the facilities available to support safe conduct of the research; or (vi) any other part of the research that would otherwise warrant review of the proposed changes by the convened IRB.

g. **Expedited Initial and Continuing Review: Permitted Categories.** The IRB may utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk and falls within the categories on the November 9, 1998 DHHS-FDA list of research eligible for expedited IRB review.

h. **Use of Subcommittees to Support IRB Activities**

The IRB may utilize subcommittees to support IRB review activities. At the discretion of the IRB Chairperson, subcommittees may be appointed to perform expedited reviews or fulfill the duties of primary reviewers. The IRB Chairperson may also appoint subcommittees on an ad hoc basis to perform additional functions as required. Under no circumstances may a subcommittee take actions that only the full IRB is authorized to take.

i. **Review of Reports of Unanticipated Problems or Adverse Events.** Principal Investigators are required to notify the IRB promptly of any unanticipated problems involving risks to subjects or others that occur by their employees or agents by completing a TMHRI Adverse Events Form and TMHRI Adverse Events Table. Investigators are also required to report promptly to the IRB any adverse event that is reported to the FDA or the sponsor in accordance with FDA requirements.

The IRB should receive the completed IRB Adverse Event/Unanticipated Problem Reporting Form from the Principal Investigator in accordance with the following schedule:

(i) Medical Devices - For Methodist patients, investigators shall report Unanticipated Adverse Device Effects to the TMHRI IRB and study sponsor within 72 hours of becoming aware of the event.

(ii) Drugs and Biologics - Investigators shall report the to the TMHRI IRB Adverse Events that meet the following criteria:

- For all Methodist patients, and for external patients in a study as to which Methodist is the Coordinating Center, **all Serious Adverse Events and/or Unexpected Adverse Events regardless of relationship: within 72 hours** of being known. All unexpected fatal or life-threatening experiences associated with use of the drug or biologic MUST BE REPORTED IMMEDIATELY.
- For non-Methodist patients when Methodist is not the Coordinating Center, but is part of a multi-site protocol, an Adverse Event that is **both a Serious Adverse Event and an Unexpected Adverse Event and which, in the Principal Investigator's opinion, more likely than not is related to the research procedures:** within 10 days of being known.

All such reports are reviewed by an Adverse Event Review Subcommittee approved by the Chairperson. If the event is determined not to be related to the research or not serious, and if the event does not require a change in the informed consent document, the Subcommittee documents this determination in writing. The report with documentation of the Subcommittee's determination is placed in the IRB Research Application (Protocol) file and listed in the minutes of the next IRB meeting.

If, in the judgment of the Subcommittee, the event may warrant more than a minor change in the protocol or informed consent process, the Subcommittee will refer the event to the convened IRB for review and to the IRB Chairperson who may, in the period before review by the convened IRB, require modification or suspension of research activities as deemed necessary to eliminate apparent immediate hazards to subjects.

During the convened review, the IRB determine whether the research will be permitted to continue as proposed or whether changes are required. If the research will continue, the IRB also should determine whether a consent form revision is required and to what extent re-consenting and/or subject notification about new information is warranted. The IRB has the authority to suspend the research if it has significant safety or other concerns.

Regardless of the type of review (expedited or convened), the Principal Investigator will be notified in writing of the IRB's determinations, even if no further action is necessary on the part of the Principal Investigator.

It is the responsibility of the IRB Chairperson to provide prompt written notification to TMHRI's Director of the Office of Research Protection of any unanticipated problems involving risks to subjects or others, and of the resolution of those problems. It is the responsibility of TMHRI's Office of

Research Protection to provide written notification to relevant Federal Agencies, including OHRP and FDA (for FDA-regulated research) of any unanticipated problems involving risks to subjects or others, and of the resolution of these problems.

j. **Review of Sponsor or Cooperative Group Adverse Event or Safety Reports.** Principal Investigators are required to forward adverse event or safety reports issued by sponsors or cooperative groups to the IRB in accordance with TMHRI Procedure RE43. Each report should be accompanied by the completed IRB Adverse Event/Unanticipated Problem Reporting Form.

The IRB review of such reports is handled in the same manner as internal reports of unanticipated problems or adverse events.

k. **Review of DSMB Reports.**
Principal Investigators are required to forward DSMB reports to the IRB in accordance with TMHRI Procedure RE43. The review of DSMB reports is handled in the same manner as internal reports of unanticipated problems or adverse events. Data Safety and Monitoring in Research is governed by TMHRI Official Procedure RE-08.

When a DSMB is employed, the IRB may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

l. **Review in Emergency Situations.** DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. **When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject.** Such emergency care may not be claimed as research, nor may any data regarding such care obtained when there was no IRB approval be included in any report of a prospectively conceived research activity. When emergency care involves investigational drugs, devices, or biologics, FDA requirements must be satisfied.

m. **Outcomes of IRB Review.** The IRB will notify investigators in writing of its determinations in the form of a memorandum from the IRB which includes, at minimum, the following information (where appropriate): investigator name, title of study, IRB number, level of risk as determined by the IRB, approval date, continuing review interval, and any changes to the materials submitted in order to secure approval.

n. **Revisions to Protocols.** No changes in approved research (including all study

procedures, subject recruitment materials, advertisements and informed consent documents and procedures) may be initiated without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects. No research may be continued beyond the IRB approval period.

o. **Expiration of Approval Period.** The IRB is required to conduct substantive and meaningful continuing review of research not less than once per year. Thus, for research requiring review by the convened IRB, the IRB approval period may extend no more than 365 days after the convened meeting at which the research was last approved. For research within categories appropriate for expedited review, the IRB approval period may extend no more than 365 days after the expedited review at which the research was last approved.

The regulations permit no grace period and no exceptions to this one year requirement. Research that continues after the approval period expires is deemed to be research conducted without IRB approval.

Consequently, the IRB will automatically suspend the enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the subjects.

p. **Suspension or Termination of IRB Approval.**

The convened IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unanticipated problems or serious harm to subjects. The IRB will notify the Principal Investigator in writing of such suspensions or terminations and will include a statement of the reasons for the IRB's actions. The Principal Investigator will be provided with an opportunity to respond in person or in writing.

Where the IRB Chairperson determines that such action is necessary to protect the rights and welfare of subjects, the IRB Chairperson may require an immediate, temporary suspension of enrollment of new subjects or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

TMHRI's Director of the Office of Research Protection will promptly notify relevant Federal Agencies, including OHRP and FDA (for FDA-regulated research) of the suspension or termination of IRB approval as described in this section and in the preceding section dealing with suspension of enrollment of new subjects in ongoing research that does not receive continuing review and approval.

Chapter 10.
IRB Review and Approval Considerations

Federal regulations at 45 C.F.R. § 46.111, FDA regulations, and the Federal Policy (Common Rule) delineate specific criteria for the approval of research. The IRB will determine that all of the following requirements are satisfied before approving proposed research.

a. Levels of Risk. The IRB must consider the overall level of risk to subjects in evaluating proposed research, and investigators are required to minimize risks to subjects in relation to research benefits. In general, the regulations require that the IRB distinguish research that is "greater than minimal risk" from research that is "not greater than minimal risk." Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under Federal regulations at 45 C.F.R. § 46.102(i), 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.

b. Risks Minimized. In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures that are already being performed on the subjects for diagnostic or treatment purposes.

In order to ensure adequate protocol design and thus subject protection, the IRB may seek opinions from consultants on proposed research and its design. The IRB may determine that proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, ensure equitable subject selection, minimize undue influence or coercion, or otherwise to protect subjects.

All key research personnel listed on a protocol must go through a formal credentialing process through the TMHRI Office of Research Protection prior to undertaking any research activities, in accordance with TMHRI Official Procedure RE-13. Overall, the research team must possess the professional and educational qualifications, as well as the resources, to conduct the research project and to ensure that the rights and welfare of subjects will be protected.

c. Risks Reasonable Relative to Anticipated Benefits. In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB shall consider the research plan, including the research design and methodology, to determine whether it would place subjects at unnecessary risk. The IRB should consider only those risks and benefits that result from the research, and should not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

d. **Equitable Selection of Subjects.** In order to approve research, the IRB must determine that the selection of subjects is equitable. In making this determination, the IRB should evaluate the purposes of the research and the research setting, and should be especially cognizant of the problems of research involving vulnerable subject populations.

The IRB should carefully examine inclusion-exclusion criteria and recruitment procedures in order to ensure that the burdens and benefits of the research are being distributed equitably. The IRB should be mindful of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to individual subjects or the groups to which they belong.

In addition, the IRB should be mindful of the desirability of including both women and men as research subjects and should not arbitrarily exclude the participation of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

Principal Investigators in particular must provide details of the proposed involvement of humans in research, including the characteristics of the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review numbers are not included in the background data for a protocol, the investigators must provide a clear rationale for omission of this information. For additional information, refer to Section 492B of the Public Health Service Act, and NIH Guide for Grants and Contracts, Vol. 23, Number 11, March 18, 1994.

e. **Informed Consent Procedures.** In order to approve research, the IRB must determine that legally effective informed consent will be sought from each prospective subject or the subject's legally authorized representative (see 45 C.F.R. § 46.116), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver must be consistent with applicable law. Informed consent of research subjects is governed by TMHRI Official Procedure RE-12.

f. **Documentation of Informed Consent.** In order to approve research, the IRB must determine that informed consent will be appropriately documented, unless documentation can be waived under Federal regulations.

g. Data Safety Monitoring. In order to approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects.

For research in which risks are substantial, a general description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events

When a DSMB is utilized, any IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Refer to TMHRI Procedure RE08 on Data Safety Monitoring.

h. Privacy of Subjects and Confidentiality of Data. In order to approve research, the IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and the confidentiality of data.

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

i. Additional Safeguards for Vulnerable Subjects. In order to approve research, the IRB must determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, fetuses, neonates, persons with mental disabilities, or economically or educationally disadvantaged persons.

j. Review More Often Than Annually. The IRB should consider the following factors in determining which studies require review more frequently than on an annual basis:

(i) The probability and magnitude of anticipated risks to subjects;
(ii) The likely medical condition of the proposed subjects;
(iii) The overall qualifications of the Principal Investigator and other members of the research team;
(iv) The specific experience of the Principal Investigator and other members of the research team in conducting similar research;
(v) The nature and frequency of adverse events observed in similar research at this and other institutions;
(vi) The novelty of the research (and consequent uncertainty about the likelihood of unanticipated adverse events); and
(vii) Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period

with either a time interval or a maximum number of subjects either studied or enrolled If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year.

k. **Independent Verification From Sources Other than the Investigator of Any Information Regarding the Study, Including That No Material Changes Have Occurred Since the Previous IRB Review.** Protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator, information about various aspects of the study including but not limited to adverse event reporting, information in the scientific literature, reports of drug toxicity, drug approval status, and that no material changes occurred during the IRB-designated approval period.

The IRB may consider the following factors in determining which studies require such independent verification:

(i) The probability and magnitude of anticipated risks to subjects;
(ii) The likely medical condition of the proposed subjects;
(iii) The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed;
(iv) Prior experience with the Principal Investigator and research team; and
(v) Any other factors that the IRB deems relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, may retrospectively require such verification at the time of continuing review, or may require such verification at any time during the approval period in the light of new information.

l. **Consent Monitoring.** In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

The IRB may also require that investigators include a "waiting period" within the consent process, or employ devices such as audiovisual aids or tests of comprehension.

m. **Advertisements and Recruitment Incentives.** The IRB is required to review and approve all advertisements (including posters, announcements, notices, displays, etc.)

and recruitment incentives associated with the research that they oversee. Advertisements and incentives are directly related to the informed consent process and must be consistent with prohibitions on coercion and undue influence. Any change in an approved advertisement or recruitment incentive must be approved by the IRB prior to being put into effect.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

(i) The name and address of the Principal Investigator and/or research institution;
(ii) The condition under study and/or the purpose of the research;
(iii) In summary form, the criteria that will be used to determine eligibility for the study;
(iv) A brief list of participation benefits, if any. The possible benefits should be presented in a conservative manner without any exaggeration or excessive enthusiasm;
(v) The time or other commitment required of the subjects; and
(vi) The location of the research and the person or office to contact for further information.

Recruitment procedures should be designed to assure that informed consent is given freely and to avoid coercion or undue influence. In order to evaluate this aspect of the research, the IRB should know in general terms who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

The IRB may require that advertisements and recruitment incentives for proposed research be modified to minimize the possibility of ambiguity, coercion or undue influence in recruitment.

n. **Obtaining Consent from Non-English Speakers.** Federal regulations at 45 C.F.R. § 46.116 require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative).

In accordance with these regulations, the IRB must require that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent.

Investigators can document informed consent in either of two ways:

(i) A full-length informed consent document written in language understandable to the subject; or
(ii) A "short-form" consent document in the language of the subject that states the general elements of informed consent.

TMHRI will provide sample "short form" consent documents to investigators in languages typically encountered in Methodist subject populations. The IRB must

approve the use of any consent form for a particular study. Investigators will be responsible for creating short form consent documents in languages not typically encountered in Methodist subject populations.

If investigators use the "short form" to document informed consent, they must also provide subjects with (i) the full-length informed consent document in English, and (ii) a interpreter who can take part in the oral informed consent conversation to ensure subject understanding and who may serve as the witness. The "short form" consent document written in the subject's language must be signed by the subject (or the subject's legally authorized representative) and the witness. The full-length English consent document must be signed by the witness and the person obtaining consent. The subject must be given copies of both the "short form" consent document and the English consent document.

Whether a full-length or a "short form" consent document is utilized, the IRB will require that appropriately translated documents be submitted to the IRB for review and approval prior to their use in enrolling subjects.

o. **Payment to Research Subjects.** The IRB will review any proposed payments to research subjects associated with the research that they oversee. Payments to research subjects may not be of such an amount as to result in coercion or undue influence on the subject's decision to participate. Payments may not be provided to subjects on a schedule that results in coercion or undue influence on the subject's decision to continue participation.

The IRB will review all proposals involving the payment of subjects (in excess of reimbursement for travel) in light of these guidelines. Payments to subjects must be made from approved funds.

p. **Compensation for Injury.** The IRB will ensure that subjects are provided with accurate information about the availability of compensation and/or treatment for injury occurring in the research that it reviews.

q. **Certificates of Confidentiality.** In rare cases in which research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes.

In such situations, the IRB may require that an investigator obtain a DHHS Certificate of Confidentiality ("CoC"). A CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

A CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA

for audit purposes. Consequently, it is important for Principal Investigators to inform subjects beforehand of the conditions under which the Principal Investigators will voluntarily or may be legally required to disclose information to third parties. The IRB will require that these conditions for disclosure be stated clearly in the informed consent document.

Information concerning CoCs can be obtained from any of the following websites:

http://www.nimh.nih.gov/research/confident.cfm
http://www.niaaa.nih.gov/extramural/confidential.htm
http://www.nida.nih.gov/funding/confidentialityfaq.html
http://www.hrsa.gov/quality/certconf.htm
http://cancertrials.nci.nih.gov/researchers/safeguards/certificates/index.html
http://www.nhlbi.nih.gov/funding/policies/certsinfo.htm

r. **Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research.** Federal regulations at 45 C.F.R. § 46.116(d) permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

(i) The research involves no more than minimal risk to the subjects;
(ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(iii) The research could not practically be carried out without the waiver or alteration; and
(iv) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and the bases for the findings will be clearly documented in IRB minutes when the IRB exercise this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the TMHRI IRB will not approve such alterations or waivers for FDA-regulated research.

s. **Waiver or Alteration of Informed Consent Requirements: State or Local Public Benefit Programs.** Federal regulations at 45 C.F.R. § 46.116(c) permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether, for certain research approved by government officials that relates to evaluation of public benefit or service programs. In order to approve such a waiver or alteration, the IRB must find and document that the research could not practicably be carried out without the waiver or alteration and meets the requirements of 45 C.F.R. § 46.116(c). These findings and the bases for the findings will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

t. Waiver of Documentation of Consent. Federal regulations at 45 C.F.R. § 46.117(c) permit an IRB to waive the requirement to obtain written documentation of informed consent. In order to approve such a waiver, the IRB must find and document **either** of the following conditions:

(i) 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. In this case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(ii) The research presents no more than minimal risk of harm to subjects and involves no procedures or activities for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

These findings and their bases will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

Chapter 11.
Required Elements of Informed Consent

Investigators must obtain the legally effective informed consent of the prospective subject, or the subject's legally authorized representative, before the subject can be included in research and before investigators can perform any research-related procedures, unless the IRB expressly waives this requirement. TMHRI Official Procedure RE-12 governs informed consent.

Informed consent presumes informed decision-making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits so that they are able to reach an **informed decision** as to whether they will **voluntarily participate**.

To ensure an effective informed consent process, Federal regulations at 45 C.F.R. § 46.116(a) and FDA regulations mandate the inclusion of eight basic informed consent elements. Informed consent must include each of these basic elements, unless the IRB has specifically approved an alteration or waiver of one or more of these elements. The IRB may routinely, or on a case-by-case basis, require that additional information, beyond these eight basic elements, be included in the informed consent. These elements are set forth in TMHRI Official Procedure RE12.

Legally Authorized Representatives. Federal regulations do not specify who may serve as a subject's legally authorized representative. State law makes this determination. The standards under which a subject's representative may provide legally effective informed consent for research may be more stringent than for medical treatment. The Methodist Department of Legal Services should be consulted on any questions regarding the use of legally authorized representatives.

Chapter 12.
IRB Review of FDA-Regulated Research: Investigational Drugs, Devices, and Biologics

The FDA is the component of DHHS that is responsible for implementing and enforcing the Federal Food, Drug, and Cosmetic Act ("FD&C Act") to regulate the safety and efficacy of drugs, devices and biologics intended for human use.

The FDA regulates, among other things, clinical investigations that are conducted on drugs, biologics, and devices. All such investigations typically must be conducted in accordance with FDA requirements for clinical investigations, informed consent and IRB review.

Clinical trials involving an investigational drug, device, or biologic that are supported by DHHS (*e.g.*, the National Institutes of Health) fall under the jurisdiction of both the FDA and OHRP. Such trials must comply with both the FDA and the DHHS human subject regulations (including, of course, the Common Rule).

a. FDA vs. Common Rule and DHHS Requirements

The human subject protection requirements found in FDA regulations and DHHS regulations are substantially the same as the Common Rule requirements. However, there are important differences. Among the differences are, for example:

- FDA regulations contain no Assurance requirement;
- FDA regulations at 21 C.F.R. Parts 50 and 56 apply to "clinical investigations," whereas DHHS regulations at 45 C.F.R. Part 46 apply to all research involving "human subjects";
- Conditions for exemption, exception, and waiver of IRB review and Informed Consent requirements differ;
- FDA regulations require specific determinations for IRB review of device studies (see below);
- FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule or DHHS regulations;
- DHHS regulations include specific additional protections for pregnant women, fetuses, and human neonates (Subpart B) and prisoners (Subpart C) that are not contained in the FDA requirements; and
- FDA's regulatory definitions of the terms "human subject" and "clinical investigation (research)" differ from the Common Rule definitions of those terms.

b. Investigational Drugs, Devices, and Biologics

Applications are submitted to FDA for approval of research involving investigational drugs, devices, and biologics as follows:

IND (including biologics). An IND permits a drug that otherwise would be required to comply with premarketing approval requirements to be shipped lawfully for the purpose of conducting clinical investigations of that drug. FDA's primary objective in reviewing an IND is to assure the safety and rights of subjects, and in later clinical phases, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Thus, an IND must be submitted to FDA prior to the commencement of any clinical trial conducted in support of a potential New Drug Application. An IND goes into effect 30 days after submission to FDA unless the agency has questions or comments about the submission. An IND generally consists of the initial chemistry, analytical, formulation, and animal testing data generated during the drug's preclinical phase, as well as detailed information about the study protocol, investigator, and any prior human experience with the drug. In addition, the submission and approval of an IND is required in order to initiate research on biological products, which include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

IDE. An IDE permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. Most IDEs are conducted to demonstrate the safety and effectiveness of a device that requires approval of a Pre-Market Approval application ("PMA"). In some instances, clinical data must be generated to support a claim of substantial equivalence for a premarket notification submission, otherwise known as 510(k).

c. Clinical Investigator Responsibilities

Under FDA regulations, the Principal Investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. Each Principal Investigator must accept specific responsibilities that include the following:

- Ensuring conduct of the research according to the investigator agreement, investigational plan (protocol), and all applicable regulations;
- Obtaining initial and continuing IRB review and approval and reporting to the IRB as required;
- Protecting the rights, safety, and welfare of the research subjects in accordance with 21 C.F.R. Part 50 (which includes obtaining the informed consent of each subject);
- Training and supervising all members of the research team;
- Controlling access to, use and disposition of the test article (drug / biologic / device);
- Monitoring and reporting adverse events;
- Maintaining and retaining accurate records; and
- Ensuring compliance with financial disclosure requirements.

d. Sponsor Responsibilities

The sponsor of a clinical investigation initiates and holds the IND or IDE for a clinical investigation. Although the Sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be a sponsor for an investigation. A Principal Investigator is referred to as the sponsor-investigator when the Principal Investigator is also the initiator of the clinical investigation.

The responsibilities of sponsors and sponsor-investigators include the following:

- Maintaining an effective IND or IDE;
- Obtaining qualified investigators and monitors;
- Obtaining approval of investigator agreements;
- Providing necessary information and training for investigators;
- Monitoring the investigation and terminating it if necessary;
- Controlling the investigational product, including the disposition of unused supply;
- Reporting significant adverse events to FDA/Principal Investigators/IRB as appropriate;
- Maintaining and retaining accurate records;
- Ensuring that IRB review and approval is obtained;
- Providing the IRB and Principal Investigators with significant new information about the investigational product and the investigation; and
- Obtaining sufficient financial information from investigators to ensure compliance with financial disclosure requirements

e. IRB Review of Medical Devices

In accordance with FDA requirements, it is the policy of IMHRI that a decision of Significant Risk ("SR") or Non-Significant Risk ("NSR") for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk vs Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

(i) **SR Device Defined.** A SR device study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant, or (2) is used in supporting or sustaining human life, or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full IRB approval and compliance with the informed consent regulations found at 21 C.F.R. Part 50.

(ii) **NSR Device Defined.** A NSR device study is one that does not meet the definition of a SR study. NSR studies must also be reviewed and approved by the IRB and require compliance with the informed consent regulations found at 21 C.F.R. Part