METHODIST HEALTHCARE

INSTITUTIONAL REVIEW BOARD

GUIDELINES
and
STANDARD OPERATING PROCEDURES

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I. *PURPOSE OF THE Methodist Healthcare Institutional Review Board:*

The purpose of the Methodist Healthcare Institutional Review Board (MHIRB) is to assure the protection of the rights and welfare of the human subjects who participate in research at Methodist Healthcare (MH).

INTRODUCTION

The conduct of research activities involving the use of human subjects, including the responsibilities of investigators and institutions where the research is being conducted, is detailed in the Code of Federal Regulations (CFR), Title 21, Sections 50, 54, 56, 312, 314, 812, 814; 45 CFR 46. "Human subject" is defined as "any individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be a healthy individual or patient."

[21CFR56.102(a)]

To ensure the rights of human subjects, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued a report entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (otherwise known as the Belmont Report). Together, the CFR and the Belmont Report impart specific duties and obligations to investigators and institutions, legally binding by the CFR and morally binding by the Belmont Report. Methodist Healthcare takes these duties and obligations very seriously.

The policy of this Institution is that all research activities on its premises shall be governed by the Methodist Healthcare Institutional Review Board (MHIRB), in accordance with the Code of Federal Regulations and the Belmont Report. This manual sets forth policies and procedures to be followed by the MHIRB and investigators in the process of planning or conducting research at this Institution.

[21 CFR 56.101(a); 21 CFR 56.102.(c)--(g); 21 CFR 56.109 (e), 45 CFR 56.104(c)]

References throughout these guidelines are to the following:

- 45 CFR 46 which applies to research involving human subjects conducted by the Department of Health and Human Services (DHHS) or supported in whole or in part by DHHS
- 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards), which apply to all research involving products regulated by the Food and Drug Administration (FDA) including research and marketing permits for drugs, biological products or mechanical devices for human use, food and color additives, or electronic products
- 21CFR312, 314, 812, 814
- The Belmont Report
- The Nuremberg Code
- The Declaration of Helsinki
- Methodist Healthcare System Policies

II. DEFINITION OF RESEARCH

The Code of Federal Regulations defines research as, '*A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.'* Activities that meet this definition are considered to be research for the purposes of these guidelines, whether or not they are supported under a program that is considered research for other purposes. Other criteria that may be useful in determining whether a planned activity may be called research include but are not limited to:

- Collection of data with the intent of reporting it in scientific publications or utilization of the data to complete a research project/study.
- Selection of a subject's therapy by using a predetermined plan that does not consider subject-specific factors or the direct welfare of the subject (such as randomization).
- Use of investigational drugs, medical devices, biologic products, procedures, diagnostic products, or electronic equipment following a pre-determined plan with the intent to gather information.

Innovative or newly introduced therapies or procedures by a physician for treatment of a subject may not require IRB approval UNLESS they involve *'research'* activities (see above). If research activities are performed using human subjects, the MHIRB must review the research project proposal. MHIRB Administration should be contacted for any questions about these situations.

Research involving a drug or biologic that has not yet reached the marketplace requires an investigational new drug (IND) application obtained from the FDA and review by the IRB. AN IND and IRB review are also required if there is:

- an increase in the dose
- a different route of administration
- longer duration of the drug or biologic
- a change in the testing population
- reason to believe that the population has different pharmacokinetic or pharmacodynamic responses from the indicated population

Further, as described in the Belmont Report "…the term 'research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or to contribute to generalizable knowledge… Research is usually described in a formal protocol that sets forth an objective and a set of procedures to reach that objective."

Thus a key aspect of research is that there be a systematic design in advance, generally utilizing a scientific approach or protocol, for the definite purpose of contributing to generalizable knowledge. However, the lack of advanced planning does not obviate nor negate the requirement of MHIRB review if any other aspect of the definition of research is evident.

The MHIRB reserves the right to review any activity that gives the appearance of research in order to protect the rights and welfare of individuals receiving care at any MH facility.

[21 CFR 56.101.(a), 21 CFR 56.102.(b), 21 CFR 56.103, 45 CFR 46.102(d)]

III. MHIRB AUTHORITY and RESPONSIBILITY

A. Authority:

The MHIRB acts by the authority of the Board of Directors of Methodist Healthcare and is designated by MH to review, to approve the initiation of and to conduct periodic review of research involving human subjects at MH. The MHIRB functions in compliance with applicable state and local laws, rules, regulations, and standards, including regulations of appropriate private and governmental accrediting and regulatory agencies that have jurisdiction over such matters. The records, minutes and proceedings of the MHIRB are confidential and protected by law.

B. Assurance of compliance:

Methodist Healthcare will comply with regulations to protect human research subjects as outlined in the FederalWide Assurance document. The Assurance is a document approved by the Office for Human Research Protection (OHRP) for a site to be engaged in Department of Health and Humans Services (DHHS) conducted or supported research. (See appendices for FederalWide Assurance document) MHIRB will comply with the Code of Federal Regulations (CFR) applicable to conducting research: 21CFR50; 21CFR54; 21CFR56; 21CFR312; 21CFR314; 21CFR812; 21CFR814; 45CFR46; and ICH Guidelines as adopted by the FDA. MHIRB will review all research, regardless of funding, source of initiation or type of research, according to the CFR.

C. Responsibilities:

The MHIRB shall review all research that involves human subjects at any MH facility prior to screening or enrollment of any subject. The principal investigator (PI) for research conducted at MH facilities must be affiliated with MH and have appropriate credentials as verified by the Medical Staff Office or other MH designated authority. At its discretion, the MHIRB may review, evaluate, and monitor research performed on subjects in outpatient settings not in a MH facility, provided that the investigator is an active member of the MH staff or Associate in good standing with MH.

The MHIRB has the authority to approve a research project, deny a research project, or request changes be made in any aspect of the research plan, data collection method, or to the proposed consent form prior to granting approval. Written notification of the MHIRB's action (including requests for additional information) will be provided to the investigator and appropriate institutional officials within a reasonable period of time following the IRB meeting. If any changes in the research project are requested, the changes must be submitted by the principal investigator in writing to the MHIRB, and the study may not commence until the changes have been reviewed and approved in writing by the MHIRB.

Research projects that have been approved by the MHIRB may be subject to review by other appropriate institutional bodies with the authority to approve, deny approval, suspend or terminate research projects in the institution. However, the disapproval, suspension or termination of any research project by the MHIRB may not be overruled by any institutional governing body or individual.

1)MHIRB approval of a research project means that the MHIRB has reviewed the research plan and agrees that it may be conducted at MH within the constraints set forth by the MHIRB and by other federal and institutional requirements. Approval is granted in accordance with §56:111 when all the following requirements are satisfied:

a)*Risks to the subject are minimized by using procedures*:
(i)consistent with sound research design that do not unnecessarily expose the subject to risk, and
(ii)already being performed on the subjects for diagnostic or treatment purpose when possible.

b) *Risks to the subject are reasonable in relation to anticipated benefits to the subject (if any) and the importance of the knowledge that may be expected to result.*
(i)Only risks and benefits that may result from the research (not risks and benefits of therapies that subjects receive even if not participating in the research) are considered.
(ii)The long-range effects of applying the knowledge gained in the research are not considered.

c)*The selection of subjects is equitable*.
(i)The IRB will take into account the purposes of the research and the setting in which the research will be conducted, with particular attention to the special problems of vulnerable populations, such as children, prisoners, pregnant women, handicapped, mentally disabled persons, or economically or educationally disadvantaged persons.

d) *Informed consent is sought from each prospective subject or their legally authorized representative in accordance with 21CFR50.*

e) *Informed consent is appropriately documented* §50.27.

f) *The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (when appropriate*).

g) *There are adequate provisions for the protection of the subject's privacy and maintenance of the confidentiality of the data.*

h) *Studies involving special populations (such as children, prisoners, pregnant persons, handicapped, mentally disabled, economically or educationally disadvantaged persons who might be vulnerable to coercion or undue influence) have safeguards in place for their protection.*

The MHIRB may place restrictions or stipulations on any part of the research to ensure that the welfare and rights of the subject are protected.

2) Denial of MHIRB approval for a research project may occur if:
a) Any of the above conditions (Section III. C.1) are not met.
b) Report(s) of prior investigations using the test article are inadequate to support the conclusion that it is reasonably safe to initiate the investigation in human subjects.
c) The investigator does not possess the clinical expertise, training, or experience required to investigate the efficacy and safety of the test article and ensure the safety of the subject.
d) The facilities (i.e., clinical laboratory, radiology, etc.) and/or medical support available at the institution are not adequate to ensure subject safety or that the study will be executed according to the investigational plan.
e) The project does not conform to FDA, institutional or MHIRB requirements.
f) The materials submitted to the IRB contain inaccurate information.
g) The research exposes the subject to undue risks.

The MHIRB decision to deny approval to a new research project will be communicated to the investigator and appropriate institutional officials via a written communication outlining the reason(s) for the action. The investigator has the opportunity to address the concerns in a written or verbal statement to the MHIRB.

D. Continuing Review:

The MHIRB has the authority to conduct continuing review of research involving human subjects at a time interval appropriate to the degree of risk to the subject. The risk classification assigned to the research will be utilized to assist in determining the review period assigned to the research. At a minimum, review is required annually, from the date of first approval.

E. Monitoring of Research:

The MHIRB has the authority to monitor and/or audit a research project to assure conformity with the investigative plan as well as federal, institutional, and MHIRB requirements, and that the rights and welfare of the human research subjects are protected. The MHIRB has the authority to observe, or designate a third party to observe at any time during the research the consent process or any aspect of the research. The MHIRB may also require information of any nature, including progress reports, from the investigator at any time.

F. Termination/Suspension of Research:

The MHIRB has the authority to terminate or suspend IRB approval of an ongoing research project if:

1) The project is not being conducted according to the research plan, and in accordance with federal, institutional, and MHIRB guidelines. Serious or continuing non-compliance with FDA of MHIRB regulations will be promptly reported in writing to the FDA and appropriate institutional officials.
2) The research has been associated with serious harm to subjects, and exposes them to undue risks.
3) The materials submitted to the MHIRB were found to contain inaccurate information that was essential to the IRB's decision.
4) Information required for continuing review, the investigation of adverse events, changes in the research plan, or any other information requested by the MHIRB is not accurate, adequate or submitted in a timely manner.

The suspension or termination of an ongoing research project will be promptly communicated to the investigator, appropriate institutional officials and the FDA (if an FDA approved product) via a written communication outlining the reason(s) for the action. The investigator has the opportunity to address the concerns in a written or verbal statement to the MHIRB. Subjects currently enrolled in the project will be withdrawn in a manner consistent with protecting their rights and welfare without detriment to their well-being. Follow-up visits by subjects may be permitted/required by the MHIRB to ensure the safety and best interest of the subject.

[21 CFR 56.102 (m); 21 CFR 56.103, 21 CFR 56.108, 21 CFR 56.109, 21 CFR 56.111, 21 CFR 56.112, 21 CFR 56.113, 45 CFR 46.101(a), 45 CFR 46.102(h), 45 CFR 46.103(b), 45 CFR 46.109, 45 CFR 46.111, 45 CFR 46.112, 45 CFR 46.113]

IV. MHIRB RELATIONSHIPS

A. MHIRB Relationship to institutional administration:

The MHIRB is authorized by the MH Board of Directors and reports its actions to the Board via the President and CEO of MH. The MHIRB Administration operationally reports via the Administrative Director/Administrator, Human Protections to the institutional signatory official or designee. Operational issues, budgetary matters, personnel issues and other administrative issues that arise in the MHIRB Administration are handled following hospital/system policies and procedures.

B. MHIRB Relationship to other institutional bodies:

The MHIRB and MHIRB Administration maintain a cooperative and coordinating relationship with other departments/internal entities including, but not limited to: finance, purchasing, compliance, legal, nursing service, HIM, operating room services, hospital administration (University, North, Germantown, South, LeBonheur, regional hospitals), research administration, laboratory, communications/marketing. Communication occurs in both directions and the MHIRB distributes materials as appropriate to key individuals necessary for the initiation of MHIRB approved research.

C. MHIRB Relationship to research investigators:

The MHIRB maintains a cooperative relationship with investigators and their coordinators and seeks input from investigators prior to major changes in procedures of the MHIRB.. The MHIRB provides each new investigator with an MHIRB Investigator's Packet that contains pertinent information from the MHIRB regarding procedures and responsibilities. The MHIRB also maintains a listing of Study Coordinators and supplies the coordinators with schedules of MHIRB meetings and other information regarding changes or updates as appropriate. Investigators, however, do not appoint nor participate in the selection or appointment of MHIRB members or the hiring of MHIRB Administrative support staff.

D. MHIRB Relationship to outside agencies:

MHIRB Administrative support staff belong to and participate in professional organizations. The MHIRB cooperates with other institutions/agencies regarding educational endeavors, but does not provide access to MHIRB files unless under direct legal requirement. The MHIRB cooperates with third party sponsor monitors/auditors only upon proper identification and documentation of the activity and determination that the activity is warranted. The MHIRB does not recognize the jurisdiction of other IRBs for research being carried out at MH, but does consider during deliberations the actions of other IRBs regarding a research protocol or element of the protocol, such as actions regarding an amendment or adverse event.

E. MHIRB Relationship to regulatory agencies:

The MHIRB fully cooperates with the FDA, OHRP and other duly appointed regulatory agencies in the oversight of research at MH. The MHIRB attempts to carry out regulations as stipulated in the Nuremberg Code, the Belmont Report, the Code of Federal Regulations, the Declaration of Helsinki, the applicable parts of the ICH Guidelines and local and state requirements. The MHIRB complies with legal requirements as indicated upon counsel of MH Legal Affairs.

F. MHIRB Relationship to UTIRB and St. Jude IRB:

MH and the University of Tennessee operate under a mutually agreed upon and duly executed cooperative agreement in order to reduce duplicity of IRB review and outline the jurisdiction of each IRB with respect to MH subjects. The UTIRB shall be the primary IRB for all pediatric protocols conducted at MH. The MHIRB shall be the primary IRB of record for all

protocols utilizing MH adult patients or MH facilities.

A mutually agreed upon and executed cooperative agreement exists between the UTIRB, St. Jude IRB and MHIRB. All pediatrics research at MH remain under the jurisdiction of the UTIRB. The agreement facilitates review of research initiated through St. Jude and conducted at Le Bonheur.

Copies of both cooperative agreement documents are available in the MHIRB Administration.

G. MHIRB Relationship to research subject:

The MHIRB exists to protect the rights and welfare of the research subjects at MH. In the event of a complaint from a research subject, the MHIRB will initiate an inquiry to review the perceptions and actions surrounding the incident, address any injustice that may have occurred and mediate dialogue between the investigator and the subject. The MHIRB Chairman will direct the inquiry process and seek to identify the truth about the research related complaint through fact finding efforts and processes. The Chairman will also act as facilitator for all deliberations and communications. All aspects of the inquiry will be reported to the full MHIRB.

V. MHIRB MEMBERSHIP

A. Number of Members:

The MHIRB is composed of not less than seven individuals appointed by the MH President upon recommendation by the MHIRB Chairperson.

B. Qualification of Members:

MHIRB members should possess the qualifications of:

1. commitment to ensuring the safety and welfare of human subjects
2. commitment to review research with all due diligence
3. commitment to research at MH
4. willingness to attend MHIRB meetings and actively participate in discussions
5. willingness to attend/participate in training/educational opportunities

C. Composition of MHIRB Membership:

The Board will not consist entirely of individuals from the same profession, entirely of men or women, and no selection of an IRB member shall be made based solely on gender. Investigators cannot select nor participate in the selection of MHIRB members.

The membership shall:

- be of varying personal and professional backgrounds to promote a complete and adequate review of research activities commonly conducted at MH. If research involving the inclusion of vulnerable categories of subjects (such as pregnant women, children, prisoners, handicapped, or mentally disabled persons) is regularly reviewed, individuals with experience in working with those subjects will be added to the MHIRB.
- be sufficiently qualified through experience and expertise, and of sufficient diversity, including race, gender, cultural background and sensitivity to issues such as community attitudes, to promote respect for its advice and counsel.
- contain one or more member(s) qualified to ascertain the acceptability of the research proposal considering MH commitments and policies, applicable laws, and standards of professional conduct and practice. MH legal representative is to serve as a non-voting MHIRB member in this capacity.
- contain one or more member(s) whose primary concern(s) is/are in the scientific area, and one or more members whose primary concern(s) is/are not in the scientific area.
- contain at least one member unaffiliated with MH or who does not have an immediate family member affiliated with MH.

D. Alternate MHIRB Members:

Alternate MHIRB members must meet the same qualifications as active members and be appointed by the MH President. Alternate members serve in the absence of a voting member with full voting rights and privileges for a given time period based on the time the active member is to be absent. Alternate members serving as active members will receive all documents and materials prior to MHIRB meetings and other communiqués in place of the absent member. Only duly appointed alternate members are allowed to serve in the absence of a voting member.

E. Member Duties/Responsibilities:

1. Members are appointed by the MH President upon recommendation by the MHIRB Chairman.
2. Reappointment is automatic every January unless the member requests removal from the MHIRB or the member is removed for other reasons.
3. Following appointment, members shall have voting authority in the rendering of decisions.
4. MHIRB members may be assigned to various review teams and/or ad hoc groups as needed in order to facilitate the responsibilities of the IRB.
5. Each member is expected to attend at least 70% of the designated MHIRB meetings.
   - Members shall notify the MHIRB Administration prior to the IRB meeting if they are unable to attend the meeting, and the MHIRB meeting minutes will reflect an excused absence.
   - When a member fails to notify the MHIRB Administration that they will not attend an MHIRB meeting, the MHIRB meeting minutes will reflect an unexcused absence.
   - Members with greater than 30% absences for the calendar year may be removed from the MHIRB by the MH President upon recommendation by the MHIRB Chairman.
6. Each member is to review with due diligence all materials prior to MHIRB meetings to ensure that the welfare and rights of the research subject are protected.
7. Members are expected to actively participate in the MHIRB meetings by listening to all presentations, asking questions and discussing issues.
8. Members must recognize and declare when they have a conflict of interest.
9. Members are to vote their conviction on the presented issues/studies.

F. Compensation of MHIRB Members:

Members shall not receive compensation for their services. Non-affiliated, community members may receive reimbursement for mileage and parking when attending MHIRB meetings. All members will be reimbursed for expenses related to education and training as related to the IRB.

G. Liability Coverage for MHIRB Members:

Methodist Healthcare maintains Professional/Comprehensive General Liability coverage with a limit of at least $1,000,000 for each and every claim. This applies on a blanket basis to all entities. This insurance extends to all employees, volunteers, directors, committee members and board members of all Methodist entities. In addition, an Umbrella policy remains in place with sufficient limits of liability. Both layers of insurance would cover members on Methodist Healthcare's IRB acting in their scope as volunteers. Additional information is available through MH Legal Affairs.

H. Committee Participation:

The MHIRB will designate **initial** review of all protocol revisions, study reapprovals, study closures, safety and local adverse events, correspondence, protocol violations, and any other study related information to the Advance Review Committee (ARC). The ARC will be composed of the MHIRB Chairman, MHIRB Administrative Director and at least one MHIRB pharmacy member. The ARC will review the above study related materials and compile the reports for each activity that will be reviewed by the full MHIRB. The ARC can solicit additional information from the PI and make recommendations to the full MHIRB regarding the disposition of the materials. The ARC cannot act independent of the full MHIRB and does not have the authority to approve or disapprove any submitted/reviewed materials.

VI. MANAGEMENT OF THE MHIRB:

A. Chairman

1. Appointment:

The MHIRB Chairman is selected and appointed by the MH President and serves until the Chairman asks to be removed or the Chairman is removed by the MH President.

The MHIRB Chairman is a voting member and considered when establishing a quorum.

2. Responsibilities related to:

a. MHIRB meetings:
- review agenda items for MHIRB meetings prior to agenda preparation
- review all materials considered for review at each MHIRB meeting prior to each meeting
- discuss with MHIRB Administrative Staff the MHIRB meeting prior to each meeting
- chair all MHIRB meetings
- meet with MHIRB Administrative Staff as needed in preparation for MHIRB meetings or as needed

b. MHIRB correspondence:
- review, revise as necessary and sign all correspondence related to each IRB meeting with 2 working days post each IRB meeting or delegate to designee
- review, revise as necessary and sign all miscellaneous correspondence from the IRB that may occur between meetings or delegate to designee

c. Adverse Events occurring at Methodist Healthcare:
- review all incidents reports involving subjects at Methodist within 24 hours of MHIRB receiving report
- communicate with PI if action needed; otherwise report review to Administrative Staff for inclusion in monthly report to full MHIRB

d. MHIRB members:
- maintain open communication with all MHIRB members
- recruit members as needed
- assist in providing educational opportunities for members
- discuss attendance issues with members as needed and recommend removal of noncompliant members

e. Advanced Review Committee (ARC) of MHIRB:
- review all reports generated by Administrative Staff from materials submitted from studies (includes, but is not limited to, Significant Revisions, Correspondence, Adverse Events at Local Site, Safety Reports, Closures, Reapprovals, Protocol Deviations)
- participate in monthly or as needed ARC meetings and provide guidance as necessary

f. Investigators:
- maintain open communication with investigators
- support audits of MHIRB studies with follow-up as needed with investigators
- confront investigators who are noncompliant with regulations/MHIRB policies and work to resolve issues
- assist in continuing education component for investigators

g. MHIRB Administrative Staff:
- support staff in their administration of MHIRB policies and procedures
- provide guidance as needed
- maintain open communication with staff and support their efforts in carrying out day-to-day operations of MHIRB

h. The Code of Federal Regulations (CFR):
- maintain a working knowledge of CFR and other guiding sources
- seek to enhance knowledge of issues confronting research and MHIRB and remain current on latest IRB/research/ethical developments

i. Miscellaneous:
- review all emergency use requests in accordance with CFR, MH and MHIRB policies/procedures
- participate in other activities/reviews as the need arises

B. Training of IRB Chair and Members:

1. MHIRB members shall be provided with a copy of the MHIRB Guidelines and training materials to assist them with their service on the Board.
2. Distribution of educational materials at each MHIRB meeting will assist in continuing education of members. Educational components will be presented at MHIRB meetings.
3. IRB members may be asked to attend IRB-related national and local meetings each year.
4. On-line training opportunities/sites will be made available to members.
5. MHIRB members will receive a copy of the Nuremberg Code, the Belmont Report, the Declaration of Helsinki, 45CFR46, MH System Policies governing research. Copies of all CFR and other regulatory guidelines are available to all members in the MHIRB Administration. MHIRB members are provided with the internet web addresses for all regulatory agencies governing research (FDA, OHRP, CFR).

C. Conflict of interest:

1. Conflict of interest is defined by MH System Policy S-05-032 as "a situation which may divide an Associate's objectivity, loyalty or obligation to other Associates or institutions dependent upon their most sincere efforts."
2. The following declaration of conflict of interest will be printed on each MHIRB meeting agenda: "If a board member has a conflict of interest (personal, professional or financial) relating to an item on the agenda, System policy requires the member to recuse him/herself from discussion and vote and if appropriate, to leave the room during discussion."
3. At the beginning of each MHRB meeting, MHIRB members will be asked to declare any conflict of interest and will be recused from voting on the item in conflict.
4. Members submitting their own research or serving as co-investigators or listed on the FDA 1571, 1572 or Medical Service Agreement of a study, may be present during discussion of those research projects. However, following the initial presentation of the research study at the MHIRB meeting, the investigator will be asked to exit the room. They will not be present during the deliberations by the MHIRB nor vote on any business concerning those research projects. During review of research for reapproval, revisions or amendments or any other related action items, the MHIRB member who is involved in the research may not be asked to leave the room, but will not vote.
5. MH Legal Affairs will send an annual conflict of interest statement to each MHIRB member for review, completion and return to MH Legal Affairs. Full disclosure of any situation in doubt is to be made.

D. Use of Consultants:

The MHIRB may, at its discretion, invite individuals with competence in particular areas to assist with the review of issues or research studies that require expertise beyond that available on the MHIRB. These individuals may be asked to provide written or verbal information and feedback regarding the research to an MHIRB review team or to the full MHIRB, but will not vote. The consultant may be asked to address the full MHIRB during an MHIRB meeting regarding various aspects of a research study/protocol germane to his/her field of expertise. The consultant may participate in the discussions, but may not vote.

In the event a prospective research study involves the use of a vector or is deemed to pose a significant biological threat to safety, a biological safety officer will be appointed from the University of Tennessee. This biological safety officer will adhere to published, nationally accepted standards and review the initial study application and all related initial submissions and subsequent revisions, adverse events and safety reports specific to the study.

E. Administrative Support Staff:

The MHIRB is supported by three (3) full-time positions, an Administrative Director/Administrator, Human Protection, (2) IRB Coordinators. These positions are devoted to the day-to-day operations of the MHIRB and report via the Administrative Director to Senior Management of Methodist Healthcare. The signing of MHIRB related correspondence may be delegated from the Chairman to the Administrative Director of the MHIRB or a designee at the discretion of the Chairman. Job responsibilities are detailed in the specific job descriptions on file in Human Resources, Methodist Healthcare.

F. Resources to Support MHIRB:

The MHIRB is financially supported by MH with a separate cost center and budget. Office spaces for support staff, equipment and supplies for operations, filing space and other necessary materials and technical support for day-to-day operations are funded via the budget and provided by MH. Space for the MHIRB meetings, along with meal provisions are available within MH-University Hospital and procured via hospital procedures by MHIRB Administrative staff.

[21 CFR 56.107, 45 CFR 46.107]

VII. FUNCTIONS OF THE MHIRB

A. Initial and Continuing Review:

Initial Review:

Prior to initiation of any research at MH the research protocol, informed consent, advertisements/recruitment and any other documents/materials pertinent to the research must be approved by the MHIRB or granted an exemption certification. Research not meeting expedited criteria must be reviewed and approved by the full MHIRB prior to initiation. Research studies must be submitted under original signatures of both the principal and co-principal investigators.

The principal or co-principal investigator submitting studies for full MHIRB review must personally attend the designated IRB meeting to present the research and answer questions by the IRB. Only the principal or co-principal investigator may present the study to the MHIRB. If the study involves interventions, treatment, diagnostics, investigational drugs or devices, the PI and Co-PI must be MH staff physicians and one of these must present the study to the MHIRB. Residents are not allowed to present interventional or diagnostic studies.If the PI or Co-PI is not abailable to present the study, the study will not be considered at that MHIRB meeting and will be rescheduled for presentation.

Research projects may be approved for no more than one year from the date of initial approval based on the risk determination. (See section C for risk determination criteria.)

Continuing Review:

At the date of initial approval of a research project, the project is assigned an MHIRB study number, review cycle and expiration date. Prior to study expiration, documentation for reapproval consideration must be submitted by the investigator to the MHIRB utilizing the Project Review Form. Projects initially approved by full board review require full board review for reapproval. Projects initially approved by the expedited process may be reviewed for reapproval via the expedited process. However, the standard practice of the MHIRB is to review all reapprovals at the full MHIRB board meeting.

As a condition of a research project's continuing approval, the MHIRB reviews all research projects at a time interval appropriate to the degree of risk to the human subject, but not less than once yearly. The MHIRB may review the research and all associated documents and consents at anytime. The review cycle may also be changed at the discretion of the MHIRB if there is any concern regarding the risks/benefit ratio or safety of the subject or conduct of the study.

For consideration of continued MHIRB approval, the investigator is required to complete the MHIRB Project Review Form including the following information:

- a report on subject outcome(s) (i.e., for antimicrobial studies, # of clinical cures),
- adverse events and safety reports update and those not previously reported,
- number of subjects enrolled, withdrawn and the reason for the withdrawals, lost to follow-up, completing the study,
- copy of the current informed consent document (if the study is open to enrollment),
- list of all subjects who consented, date of consent and the name of the person obtaining the consent using the consent log (see appendix)
- list of protocol violations not previously reported,

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Failure to submit all the required information within the specified time period and prior to the project's expiration date, may result in suspension or termination of MHIRB project approval. Should this occur, the MHIRB will report the termination to the FDA(for any FDA regulated study) and institutional administration as required. The MHIRB will endeavor to notify the investigator one month prior to current approval lapsing, but **seeking project reapproval is incumbent upon the investigator.**

The MHIRB will conduct a review of the research project and has the authority to monitor, audit, or designate a third party to monitor the informed consent and research processes, and to seek information from parties other than the investigator regarding changes that may have occurred since the previous review. The MHIRB shall consider the research and may reapprove the project, reapprove pending changes, change the review period, suspend or terminate MHIRB project approval.

[21CFR56.108(a)(1); 21CFR56.109(a-f)

B. Reporting of MHIRB Action to Investigator:

Following initial or continuing review of a research project or review of changes, revisions, amendments, safety reports, adverse event reports, correspondence, protocol deviations or any other correspondence from the investigator, the MHIRB will notify the investigator in writing of the decision/acknowledgement of the MHIRB. Where specific changes are required the written correspondence will detail the required changes. If there are changes required to a research project following initial submission, the research is not allowed to commence until the changes have been submitted, verified and approved. This requirement will be included in the written communication to the investigator.

Any request of the investigator from the MHIRB, such as request for more information or cooperation in the event of an audit, will be made in writing from the MHIRB to the investigator. The Administrative Director, MHIRB, will sign correspondence as indicated unless the Chairman designates otherwise.

All written correspondence from the MHIRB to the investigator or from the investigator to the MHIRB will be filed in the MHIRB study file related to the indicated research project.

Emails, faxes, written or other study specific materials received will be logged into the related study file database (when appropriate), acknowledged, reported to the MHIRB and filed in the MHIRB study file. Telephone or face-to-face conversations related to a particular study will be recorded in a memo to record and filed in the related MHIRB study file.

[21CFR56.108(a)(1); 21CFR.109(e)

C. <u>Determination of Review Cycle of Research Projects:</u>

Investigators submitting research for initial review or continuing review by the MHIRB must complete a risk determination for the research intended. At initial review, the MHIRB reviews the risk determination declared by the PI. However, the risk determination ascribed by the investigator may not be agreed with by the MHIRB.

The risk determination scoring is as follows: (The numbers in parentheses indicate the points ascribed to that aspect.)

1. The research may result in possible harm/distress/loss in which area(s) of the subject's life? (check all that apply)
   (0) None (1) Psychological (1) Physical (1) Social (1) Economic

2. Is this study? (check one)
   (0) Non drug, non device (3) Phase I (1) Phase III
   (3) Device (2) Phase II (1) Phase IV

3. Is there a possibility of the subject being identified from participating in the study?
   (0) No (1) Yes

4. The likelihood of the subject developing toxicities/complications from the study intervention is: (check on)
   (0) None
   (1) Possible but not likely and no greater risk than in routine testing and care
   (2) Probable with a greater risk than in routine testing and care
   (3) Definite with a greater risk than in routine testing and care

The points are added to produce a risk assessment score. The MHIRB will make a deliberate determination of risk based on all evidence and information presented related to the research. The MHIRB then assigns a risk classification assessment score to the research project and along with discussions of risks-to-benefits, determines the length of approval granted and the review cycle.

At the time of submission for continuing approval, the investigator completes the risk determination and indicates whether any changes have occurred in the risk-to-benefit ratio of the research. This information is reviewed by the MHIRB at the time of consideration for reapproval. At reapproval consideration the MHIRB may maintain, shorten or lengthen the review cycle based on the information reviewed. However, the review will not be less than once yearly.

[21CFR56.108(a); 21CFR56.109(f)]

D. Additional Information Requirements:

Based on the risk classification score and the information presented during initial review of the research project, the MHIRB may require additional information from the investigator, the sponsor or other sources. The history of the research project (all revisions, local adverse events, safety reports, correspondence, protocol deviations), enrollment numbers, list of subjects enrolled, date of enrollment of each subject and person obtaining consent are reviewed by the MHIRB at the time of consideration for reapproval of each research project. Incomplete information from the investigator may preclude review and subsequent suspension or termination of the research project.

Consultants may be utilized by the MHIRB in consideration of continuing review of a research project.

[21CFR56.108(a)(2)]

E. Reporting of Changes in Research to MHIRB:

The investigator is obligated to report all changes in the research activity, including, but not limited to procedures, adverse events, enrollment change, new information and study status changes to the MHIRB in a timely manner irrespective of the timing of the project review cycle. In the case of multicenter studies using an investigational drug or device, it is understood that the investigator will be receiving from the sponsor safety reports sent to the FDA from all centers participating in any study involving that drug or device. The investigator is expected to promptly forward these reports to the MHIRB. Any reports received from Data Safety Monitoring Boards (DSMB) must be reported to the MHIRB.

A. Minor Changes

Minor changes to any aspect of the research study, of an administrative nature and that have no impact on research subjects' welfare (i.e. grammatical or typographical corrections to protocol, correction to address or phone numbers for sponsor) may be approved via MHIRB Administration. Changes made and approved by the MHIRB Administration will be reported in a written and verbal report to the MHIRB.

B. Changes that do not eliminate apparent immediate hazards to the subject

Changes in the research plan must be submitted to and approved by the MHIRB before implementation. A copy of the amendment outlining the change, the revised informed consent form, if applicable, and a letter outlining the rationale for the change(s) along with supporting documentation from sponsor (if applicable) under the PI's original signature must be submitted to the MHIRB. The MHIRB will conduct a review of the changes at the full IRB meeting. The MHIRB may approve, approve pending modification, or disapprove the changes. Written notification of MHIRB action will be sent to the investigator and appropriate institutional officials within a reasonable period of time following the IRB meeting. Changes to ongoing

studies whereby there is no more than minimal risk from the change may be considered for expedited review. All changes approved via the expedited process will be reported in written and verbal form to the MHIRB.

C. Changes that eliminate apparent immediate hazards to the subject

When a change in the investigative plan is necessary to eliminate apparent immediate hazards to the study subject, the change may be initiated before MHIRB approval is granted. However, the MHIRB should be apprised within 24 hours of the change by written letter, including a copy of the amendment, sponsor documentation/rationale for change, and revised informed consent form, if applicable. The MHIRB Chairman or designee shall review the change to verify that is it consistent with protecting the welfare for the subject. The MHIRB will review the changes at the full MHIRB meeting. The MHIRB has the authority to approve, approve with modification(s), or disapprove the change(s). Written notification of MHIRB action will be sent to the investigator and appropriate institutional officials within a reasonable time period following the MHIRB meeting. Changes will be reported in written and verbal form to the MHIRB.

[21 CFR 56.108(a), 45 CFR 46.103 (b), 45 CFR 46.110 (b)]

F. Required Reporting

The investigator will report to the MHIRB:

1. *Adverse event:* an undesirable, an unintended, although not necessarily unexpected result of therapy or other intervention.

Serious adverse event: incident/episode when the subject outcome:

a. *results in death
b. *is life-threatening or places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred
c. *results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions
d. *results in or prolongs an existing subject's hospitalization (an overnight stay in the hospital, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation)
e. *is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis)
f. is a cancer
g. is the result of an overdose whether accidental or intentional
h. Other medical events that may result not in death, not be life-threatening or not require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the starred (*) outcomes listed previously.

Adverse Event Reporting:

A written report for **non-serious adverse events occurring in a MH subject** must be filed with the MHIRB Administration within 5 working days of discovery using the MHIRB Adverse Event Report Form. Follow-up reports regarding the incident must promptly be reported to the MHIRB. The PI should use his/her judgement when determining whether an untoward event is reportable. However, the MHIRB encourages reporting all adverse events to the MHIRB regardless of the requirements of the sponsor.

All **serious adverse events** (life-threatening events that may be due to the test article), and all fatal events, regardless of the relationship to the test article occurring in a MH research subject, must be reported to the MHIRB (written/e-mail/fax is acceptable) within 72 hours of their occurrence.

The PI must indicate the relationship of the adverse event to the study test article, intervention, procedure or significant aspect of the research. For each event, the PI will indicate if the event is:

- related
  - ✓ a strong temporal relationship that the AE was caused by the drug, device or intervention exists;
  - ✓ the AE was not produced by the research subject's clinical state
  - ✓ a known pattern of response to the drug, device or intervention exists
  - ✓ the AE disappears or decreases when the test article or intervention ceases or is removed or upon re-challenge
- probably related
  - ✓ there is a reasonable temporal relationship to the drug, device or intervention
  - ✓ the AE could not readily be produced by the subject's clinical state
  - ✓ a known pattern of response to the drug, device or intervention exists
- possibly related
  - ✓ there is a reasonable temporal relationship to the drug, device or intervention
  - ✓ the AE could not readily be produced by the subject's clinical state
  - ✓ the AE could have been caused by the drug, device or intervention, but there is insufficient information to conclude that there was definitely a relationship
- not related
  - ✓ there is no temporal relationship to the drug, device or intervention
  - ✓ the AE could have been produced by the subject's clinical state
  - ✓ the AE could have been produced by the environment or other intervention
  - ✓ the AE does not disappear when the intervention is removed nor reappear upon rechallenge

Upon receipt of all adverse events occurring at MH, the MHIRB Administration will send the report to the MHIRB Chairman for immediate review. The Chairman may require more information prior to reporting to the full MHIRB. The Chairman may also immediately suspend the research project or take action to protect the immediate welfare of the research subjects. The adverse event and any follow-up action(s) by the Chairman will be reviewed by the Advance Review Committee and reported at the next available MHIRB meeting.

The MHIRB will review the adverse event, and may require changes to the informed consent document, study procedures, suspend some or all study-related procedures pending the completion of MHIRB review or permanently terminate MHIRB project approval based upon an increased risk to the subject. The investigator may be required to submit additional information or reporting as deemed appropriate or necessary by the MHIRB

2. Sponsor Safety Reports (adverse events occurring outside of MH)**:**
The PI shall forward all safety information supplied by the sponsor to the MHRB Administration within a reasonable time period using the MHIRB Safety Report Form.

The PI must indicate the relationship of the adverse event to the study test article, intervention, procedure or significant aspect of the research. For each event, the PI will indicate if the event is:

- related
- probably related
- possibly related
- not related

See above definitions of relationship.

The MHIRB will review the safety reports and may require changes to the informed consent document, study procedures, to suspend some or all study-related procedures pending the completion of MHIRB review or permanently terminate MHIRB project approval based upon an increased risk to the subject. The investigator may be required to submit additional information or reporting as deemed appropriate or necessary by the MHIRB. The adverse event and any follow-up action(s) will be reviewed by the Advance Review Committee and reported at the next available MHIRB meeting.

[21CR56.10(a); 21CFR56.113; 21CFR312.32; 45CFR46.103)

G. Significant/Nonsignificant Research Device:

Research studies involving medical devices must adhere to 21CFR812. All investigational devices proposed for research at MH must give proof of an investigational device exemption (IDE) prior to review by the MHIRB. The MHIRB will consider the sponsor's determination as to whether the device study presents a significant risk (SR) or a nonsignificant risk (NSR). However the MHIRB will make its own determination as to whether the study presents a SR or NSR. If the MHIRB disagrees with the sponsor's or PI's determination of SR or NSR, the MHIRB will notify the PI and/or sponsor in writing.

Significant risk device studies:

Definition: potential for serious risk to the health, safety or welfare of the subject and

1) is an implant
2) is used in supporting or sustaining human life
3) is of substantial importance in diagnosing, curing, mitigating or treating disease
4) otherwise presents a potential for serious risk to the health, safety or welfare of a subject.

MHIRB responsibilities:

1) consider documentation from sponsor and investigator regarding designation of device as posing a significant risk. The MHIRB may agree or disagree with the sponsor's initial assessment of risk.
2) consider the nature of harm that may result from use of the device
3) decide if the investigation poses a SR; The risk determination will be based on the proposed use of the device in an

investigation and not on the device alone.
4) review the device study applying criteria 21CFR56.111
5) document in MHIRB minutes and in written communication to investigator the MHIRB's determination of risk

Nonsignficant risk device studies:

Definition: device not meeting the definition for a SR study or does not present a potential for serious risk to the health, safety or welfare of a subject and:
1) is not an implant
2) is not used in supporting or sustaining human life
3) is not of substantial importance in diagnosing, curing, mitigating or treating disease or otherwise prevent impairment of human health.

MHIRB Responsibilities*:*

1) consider documentation from sponsor and investigator regarding designation of device as posing a nonsignificant risk. The MHIRB may agree or disagree with the sponsor's initial assessment of risk.
2) consider the nature of harm that may result from use of the device
3) decide if the investigation poses a NSR; The risk determination will be based on the proposed use of the device in an investigation and not on the device alone.
4) review the device study applying criteria 21CFR56.111
5) document in MHIRB minutes and in written communication to investigator the MHIRB's determination of risk

[21CFR812.2(b); 21CFR812.150(b); 21CFR56.111; 21CFR812.3(m)k]

H. Auditing of Research Studies

The MHIRB has the authority to audit any research study for cause or not for cause reasons at any time during the course of the study. The audit may be conducted by the MHIRB or by a third party designated by the MHIRB. The PI and study sponsor will be notified in writing of the audit and is expected to fully cooperate by being personally accessible to the MHIRB and supplying any requested documents, study files, patient information or other information. If preliminary findings so indicate, the MHIRB may suspend the study enrollment or activities or terminate the study and appropriate action taken to ensure the safety and welfare of the subjects. The PI will be informed in writing of all MHIRB actions.

The PI may be required to appear before the MHIRB at a full MHIRB meeting or to meet with an MHIRB appointed investigative subcommittee. However, the PI may not have attorneys or other witnesses present at the meetings. The full MHIRB will be advised of all subcommittee meetings regarding the audit investigation and the outcomes of the meetings.

The MHIRB may engage any consultant, expert or outside help as is necessary to conduct the audit. If subjects are considered to be at risk because of actions of the PI,

the sponsor will be notified along with the MH Medical Staff President and appropriate action taken to ensure the safety and welfare of the subjects.

All audits undertaken, including updates, actions and correspondence by the MHIRB will be reported to the MH Administration and appropriate regulatory officials as indicated.

Upon completion of the audit, the findings will be reported to the full MHIRB and action taken accordingly. The final MHIRB decision will be reported in writing to the PI, sponsor, MH Administration and appropriate regulatory agencies.

VIII. OPERATIONS OF MHIRB

A. MHIRB MEETINGS

The MHIRB is scheduled to meet twice each month with the membership divided into two panels. However, the MHIRB is one duly constituted IRB, but with division of membership into two panels. Members may serve on one or both panels at the member's request and may change panels by notifying the MHIRB Administration prior to a meeting date and in sufficient time to receive the paperwork for the intended meeting.

At least one attendee member whose primary concern is in the non-scientific area and one attendee member whose primary concern is the scientific area, must be present to convene a meeting.

At least one community member must be present to convene the meeting.

***Note**:* The community member, a non-scientific member and a scientific must be present for a meeting to convene, regardless of the establishment of a quorum.

At the first MHIRB meeting of the month the MHIRB panel will review on a regular basis the revisions, reapproval applications, adverse events at MH, safety reports, closures, correspondence, protocol violations, expedited reviews, exemption certifications, and administrative approvals. At the second MHIRB meeting of the month the MHIRB will review any additional revisions, reapproval applications, adverse events at MH, safety reports, closures, correspondence, protocol violations, expedited reviews, exemption certifications, and administrative approvals that occurred after the first panel meeting but have been requested by the PI to be reviewed prior to the next month or which require more immediate consideration. Both panels will review new protocol submissions based on the date submitted as outlined in the MHIRB schedule of meetings and paperwork submission.

Both panels will review and vote on all audit results, revisions to MHIRB SOPs, decisions regarding disciplinary/regulatory mandated action by the MHIRB or other information/decisions that affect the MHIRB as a whole.

The MHIRB meetings will be chaired by the MHIRB Chairman or MHIRB Vice Chairman. In case of absence of both the chair and vice-chair, the meeting is to be chaired by the Administrative Director of the MHIRB. If none of these individuals are available, and a quorum is present, the MHIRB is to appoint, at the beginning of the meeting an MHIRB member from the quorum to serve as Chairman. In the event no MHIRB member is willing to serve in this temporary capacity, the meeting may not commence.

MHIRB meetings are open to attendance by nonMHIRB members. However, during the discussion and deliberation of business requiring confidentiality and privacy, such as results of audits, etc, an executive session of the MHIRB will be convened. Executive sessions are closed to outside attendance and are open only to duly appointed MHIRB members or individuals required by the MHIRB to attend.

The MHIRB meeting schedule will be distributed to all members and mailed annually to active investigators, MH Administration and posted on the MHIRB web site.

All MHIRB meetings will be conducted according to Roberts Rules of Order, DeVries,M.A., 2nd ed., 1998, New York: Signet.

MHIRB meetings other than the scheduled ones can be called by the Chairman, but must meet all the meeting requirements to convene (i.e. quorum, attendance by a community member, etc).

All MHIRB meetings will be audiotape recorded.

MHIRB vote will be required on:

1) new research studies not meeting expedited or exemption certification criteria
2) reapproval of research applications
3) revisions/amendments (includes protocol and informed consent)
4) advertisements/recruitment materials
5) termination/suspension of a study (excludes those studies closed or suspended by the investigator)
6) initiation of audit/audit recommendations
7) sanction/discipline of an investigator
8) minutes
9) SOPs
10) other items as deemed appropriate by the MHIRB or legal counsel

B. Pre-meeting information:

One week prior to each MHIRB meeting, each member of that panel will receive:

1) an agenda which identifies business to be conducted, the location, date and time of the MHIRB meeting and states the declaration of conflict of interest
2) minutes of that panel's previous meeting
3) (if any) new study materials (summary, informed consent document, advertisement if applicable, other material related to the research study under consideration as appropriate or required)
4) (if any) action items (those items requiring MHIRB vote)
5) (if any) information items (closures, adverse event, safety, correspondence, protocol violation, administrative/expedited/exemption certification reports)
6) copies of any miscellaneous items (including, but not limited to, educational component materials)
7) copy of the other panel's minutes from the previous month

C. Voting Requirements:

A quorum is required to convene an MHIRB meeting and transact business, including voting. Members may serve on one or both panels with a quorum being a simple majority (>50%) of the total membership for each respective panel. Non-voting members are not counted when establishing a quorum.

All duly appointed MHIRB members serving on a panel may vote with full voting rights.

The MHIRB Chairman is a voting member and considered when establishing a quorum.

At least one attendee member whose primary concern is in the non-scientific area and one attendee member whose primary concern is the scientific area, must be present to convene a meeting and for voting to occur.

At least one community member must be present to convene the meeting and for voting to occur.

Duly appointed alternate members may vote only when substituting for the regular member they represent.

Approval or disapproval of a research study or other action item occurs by a simple majority (>50%) vote of those present, as long as a quorum is maintained.

Should a quorum be lost during the meeting, the meeting cannot continue and business must be suspended until the quorum is restored. If the quorum is not restored the meeting must be ended. Voting cannot occur if a quorum is not present.

No member may vote on a research project in which the member has a conflict of interest as defined in the system policy regarding conflict of interest or evident in the declaration of conflict of interest of the MHIRB.

No written or telephone proxy votes will be allowed.

Research protocols will not be discussed nor considered for vote if MHIRB members have not been provided materials prior to the MHIRB meeting in adequate time to review and consider the materials. Walk-in presentations by a PI are not acceptable to the MHIRB and will not be entertained nor considered for a vote.

D. MHIRB Research Review Process:

The MHIRB shall review all research, including, but not limited to investigational drugs, medical devices, biologic products, procedures, diagnostic products, or electronic equipment, performed on human subjects at any MH facility. This review includes proposed utilization of information, tissue, samples, etc from the MH subject.

The PI must complete a New Investigator Profile and submit it along with a current CV to the MHIRB at the time of the first study submission. The PI Packet will be reviewed by the MHIRB Administration with the PI at the time of the first MHIRB submission

The principal investigator (PI) of the research must be affiliated with MH and have appropriate credentials as verified by the Medical Staff Office or other MH designated authority. The PI must submit the required materials for review of the research, which includes revisions/amendments, adverse events, safety reports, protocol violations, under his or her original signature. Correspondence may be initiated from the study coordinator or other members of the research team. However, all revisions/amendments, adverse event reporting, safety reports and protocol violations must be signed by the PI. Stamps of the PI's name will not be accepted on any documents submitted to the MHIRB.

Failure to have appropriate credentials, submit the appropriate and required materials or lack of original PI signature will delay the acceptance of documents for consideration by the MHIRB.

All research involving drugs, biologics or devices must have an IND/IDE number provided by the FDA. The PI must provide this information at the time of the study submission to the MHIRB. If no IND/IDE are required, the PI must provide supporting documentation from the FDA.

If the study involves the collection of highly sensitive and private information the investigator may obtain a Certificate of Confidentiality (COC) from the National Institutes of Health (NIH) regardless of whether a projects is federally funded. A COC protects investigators and institutions from being compelled to disclose indentifying nformation on research subjects in any federal, state, local, civil, criminal, administrative, legislative or other proceeding. The COC should be presented with the initial study submission materials.
(Source: Public Health Service Act § 301(d) [42 U.S.C. § 242 (a)]. 1988)

Research proposal submission process for all new research:
1) submission of required paperwork/written materials to MHIRB Administration by PI
2) review by MHIRB Administration for completeness of materials submitted (Any area of incompleteness is communicated to the contact person designated on the research application for correction and resubmission.)
3) determination made by MHIRB Administration, based on established CFR criteria, as to the type of review indicated:
   a) full MHIRB review or
   b) expedited MHIRB review or
   c) whether exemption certification can be granted
   (See full, expedited, and exemption certification criteria listed below.)
4) research proposal data entered into MHIRB database
5) research proposal assigned an MHIRB study number based on year of submission and sequential number of protocol submitted 6. Studies reviewed originally by the UTIRB and sent to the MHIRB under the cooperative agreement are assigned a study number designated "99" for UT, "03" for the year and "001" for the study sequence. The MHIRB will consider a UTIRB approved study for MHIRB approval upon receipt of a letter from the PI indicating that the cooperative agreement is to be evoked. All study files with a "99" designation are maintained to the specifications of MHIRB original studies.

A. EXPEDITED REVIEW process
:
Upon receipt of the following documents:
- 4 copies of the Study Summary Form
- 4 copies of the Study Protocol (including references, appendices, questionnaires, survey, tests, etc.)
- 4 copies of the Informed Consent Form following Methodist IRB guidelines
- 2 copies of the Investigator's Brochure for non-FDA approved drugs and investigational devices
- 1 copy of the Study Budget
- 1 copy of the contract (if applicable)

MHIRB Administration will check the contents of the application for completeness.

To be considered for expedited review the research proposal must:

A) involve no more than minimal risk [Federal guidelines define minimal risk as, "*The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*"] and

B) meet one or more of the following categories for expedited review as outlined in the Federal Register:

1) collection of hair and nail clippings in a non-disfiguring manner; of deciduous teeth; and of permanent teeth if subject care indicates a need for extraction
2) collection of excreta and external secretions including sweet and uncannulated saliva; of placenta at delivery; and of amniotic fluid at the time of rupture of the membrane before or during labor
3) recording of data from subjects who are 18 years of age or older using non-invasive procedures routinely employed in clinical practice. This category includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, electrocardiography, electroencephalography, thermography detection of naturally occuring radioactivity, diagnostic echography and electroretinography. This category does not include exposure to electromagnetic radiation outside the visible range (for example, microwaves or x-rays)
4) collections of blood samples by venipuncture, in amounts not exceeding 450 ml in an eight week period and no more often than 2 times per week from subjects who are 18 years of age or older and who are in good health and not pregnant.
5) collection of both supra-and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of teeth and the process is accomplished in accordance with accepted prophylactic techniques.
6) voice recordings made for research purposes such as investigations of speech defects.
7) moderate exercise by healthy volunteers.
8) the study of existing data, documents, records, pathological specimens or diagnostic specimens.
9) research on drugs or devices for which an IND exemption or IDE is not required.

[Federal Register Vol 46, No. 17 Tuesday, January 27, 1981, 56FR28029, June 18, 1991]

Once expedited criteria is established for the research proposal submitted:

1) the proposal and all submitted documents are sent to the Expedited Review Committee, consisting of the Chairman of the MHIRB, Administrative Director or designee and Legal Counsel to the MHIRB. The Committee may request consultant input as needed.
2) the Expedited Review Committee may exercise the full authority of the MHIRB,

except it may not disapprove research. All 3 members must be in agreement before the proposal can be approved.

A negative vote by any of the three members will result in:
a) denial of the expedited review status with full MHIRB review required
b) modification based on the review; required changes then may result in approval

3) actions of the Expedited Review Committee are communicated to the MHIRB in a written and verbal report to the MHIRB
4) all decisions of the Expedited Review Committee are communicated to the PI in written form
5) the research proposal, once approved by the Expedited Review Committee is assigned an MHIRB study number and a review cycle of 12 months with the expiration date set at 12 months from the action date of the Committee

The research proposal approved under the expedited process is subject to the same rules and regulations as proposals approved under full review. This includes, but is not limited to reporting of adverse events and the process for requesting changes/revisions.

B. FULL REVIEW process

Any research that exceeds minimum risk to the subject or does not meet the criteria for expedited review or exemption certification must have full MHIRB review. Federal guidelines define minimal risk as, "*The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*" This definition of minimal risk serves as a benchmark to assist with decisions about whether proposed studies are eligible for full IRB review (greater than minimal risk) or for expedited review (minimal risk).

The MHIRB reserves the right to require any research to have full MHIRB review regardless of whether expedited criteria is satisfied.

Once full review criteria is established:
1) upon receipt of the following materials:
- 4 copies of the Study Summary Form
- 4 copies of the Study Protocol (including references, appendices, questionnaires, survey, tests, etc.)
- 4 copies of the Informed Consent Form following Methodist IRB guidelines
- 4 copies of the Assent Form for research conducted on minors less than 18 years of age
- 2 copies of the Investigator's Brochure for non-FDA approved drugs and investigational devices
- 1 copy of the Study Budget
- 1 copy of the contract (if applicable)

An IND or IDE must be provided for all investigational drugs or devices prior to review by the MHRIB.

MHIRB Administration will check the contents of the application for completeness. If all the documents are complete, the MHIRB Administration will

issue the investigators a letter indicating the MHIRB reference number, MHIRB review team members and tentative data for full MHIRB review. The MHIRB Review Team is appointed to evaluate each research project and works with investigators to resolve issues and areas

The review team for all investigational drug studies will consist of a pharmacy MHIRB member and one additional MHIRB member. Other new research protocols will be reviewed by a 2 member MHIRB review team. When possible, review teams will be composed of members with an interest or understanding/expertise in the area of research.

2) MHIRB Administration will establish deadlines for completion of review by review teams and will assign a date for MHIRB presentation of the research by the PI.
3) The review team members will review the new research protocol independently, then collaborate regarding their reviews. The primary reviewer will complete the Primary Review Response form and send a copy to the MHIRB Administration for the study file and a copy to the PI.

Note: All areas required to be changed by the Primary Review Team must be changed or justified, as indicated on the form, for the research to be presented at the assigned MHIRB meeting. The review form becomes a permanent part of the MHIRB study file.

4) Upon receipt of the required changes, the MHIRB Administration will send copies of the Study Summary, the informed consent document and advertisements (if applicable) to each MHIRB members on the panel to which the presentation will be made at least one week prior to the scheduled meeting. All materials, information, memos to record or other study related materials are available to all MHIRB members at any time. Materials not initially included in the material sent to members will be copied and supplied to the MHIRB member upon request. Any study materials or reference materials will be supplied at any time upon request to any MHIRB member.
5) The PI must present the research protocol in person to the MHIRB. If the PI is unavailable, a Co-PI may present the protocol. However, for high risk protocols, only a physician PI or Co-PI may present the protocol to the MHIRB. If the PI does not attend the meeting the research protocol is tabled until the PI is available to attend. The MHIRB will not consider for approval nor take any action on a new research protocol not presented by the PI.

Note: Walk-in presentations by a PI are not acceptable to the MHIRB and will not be entertained nor considered for a vote.

7) Upon presentation of the protocol by the PI, all MHIRB members may ask questions or make comments regarding the research. The burden of presentation will be upon the PI with the review team members serving as regular voting MHIRB members.

8) Following presentation of the research by the PI, the MHIRB members will deliberate and vote on the research to:
   a) approve the research if all requirements of 21CFR56.111 are met
   b) approve the research pending modifications as specified by the final recommendation of the MHIRB at the vote
   c) table the research pending additional information/research
   d) disapprove the research
9) Based on the vote and the risk classification score, the research project is assigned a review cycle of not more than one year from the date of vote.

Note: Research projects that have been approved by the MHIRB may be subject to review by appropriate institutional bodies with the authority to approve, deny approval, suspend or terminate research projects in the institution. Examples of denial of a research project to proceed within the institution include research that would cause a potential financial loss to the institution or an anticipated negative community response to the research. However, the disapproval, suspension or termination of any research project by the MHIRB may not be overruled by any institutional governing body or individual. *[21CFE56.112]*

Following the MHIRB meeting and vote on the research the results (to approve, request additional information, table, disapprove) are conveyed to the PI in written form and a copy filed in the MHIRB study file within 5 working days following the MHIRB meeting in which the research was presented.

When appropriate, institutional officials are copied on correspondence to the PI or are notified in a separate written communiqué regarding the outcome of the MHIRB meeting and/or vote. In the event that the MHIRB rules on the significant or nonsignificant risk of a device that is different from the sponsor's ruling, the sponsor, along with the PI and institutional officials will be notified in writing within 5 working days of the MHIRB meeting. *[21CFR56.108(a)(1); 21CFR56.109(e);21CFR56.1159(a)(4)]*

Appeal of MHIRB ruling by PI:
Upon receipt of the MHIRB ruling on a research project, the PI may appeal the decision in writing. The PI may appeal:

- the final decision by the MHIRB
- any stipulation or restriction placed upon the research
- the ruling of the MHIRB as to the whether a device poses a significant or nonsignificant risk
- any other request/requirement by the MHIRB

The PI may request another meeting with the MHIRB or may put all requests for appeal along with the rationale in written form to the MHIRB.

The MHIRB will hear the PI or address the written request for appeal at the next available MHIRB meeting. The PI may not have attorneys present during any presentation to the MHIRB or during any of the appeal process. The PI may address appeals of the MHIRB ruling to appropriate institutional officials. The MHIRB will consider and rule on the appeal. In the event the MHIRB disapproves the appeal or the research, the disapproval cannot be overridden by institutional bodies or individuals. *[21CFR.112]*

IX. EXEMPTION CERTIFICATION BY MHIRB

The type of review allowed is dependent upon the potential risk the research poses to the subject and which criteria is satisfied.

An investigator may file for an exemption certification from the MHIRB if the research projects meets one of the following categories:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on:
   - regular and special educational instructional strategies, or
   - the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
   - information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
   - any disclosure of the human subjects' responses outside the research could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2 of this section, if:
   - the human subjects are elected or appointed public officials or candidates for public office; or,
   - federal statutes require, without exception, that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or 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.
5. Research and demonstration projects that are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
   - public benefit or service programs;
   - procedures for obtaining benefits or services under these programs;
   - possible changes in or alternatives to those programs; or
   - possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies:
   - if wholesome foods without additives are consumed, or
   - if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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. When the PI files a exemption certification form with the MHIRB, a determination is made by the

MHIRB Administration as to whether the proposed research meets the exemption criteria, an exemption certification is granted.

The research is given a study number by the MHIRB consistent with the year and sequential study number available.

If exemption certification is denied, the PI must submit an application for expedited or full MHIRB review before the research can commence.

At the end of one year, the PI is requested to complete an Exemption Certification Renewal form to assist in evaluating whether the research is granted a continuation of the exemption or must be reevaluated under different criteria.
The exemption certifications and continuations granted are reported in written and verbal reports to the MHIRB.

[45CFR46.101]

X. EMERGENCY USE OF A TEST ARTICLE

A. ***Definitions****:*

Emergency use: The use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. *[21CFR 56.102(d)]*

Test article: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act *[21 CFR 56.102(l)]*

B. ***Investigational New Drug (IND) Application:***

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an Investigational New Drug (IND) in the usual manner. In such cases, the FDA may authorize shipment of the drug for a specified use *[21 CFR 312.36*]. Such authorization is usually conditioned upon the sponsor making an appropriate application as soon as practicable. These studies often meet the requirement for exception from prior IRB approval. Informed consent is required unless it cannot be obtained as outlined in 21 CFR 50.23.

C. ***Obtaining an Emergency IND***

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means *[21 CFR 312.36]*. FDA contacts for obtaining an emergency IND:

Drug products: Drug Information Branch (HFD-210) 1-301-827-4573

Biological blood products: Office of Blood Research and Review (HFM-300) 1-301-827-3518

Biological vaccine products: Office of Vaccine Research and Review (HFM-400) 1-301-827-0648

Biological therapeutic products: Office of Therapeutics Research and Review (HFM-500) 1-301-827-0648

Nights & weekends: Division of Emergency & Epidemiological Operations (HFC-160) 1-301-443-1240

Address: For investigational biological drugs, inquiries should be directed to the Division of Biological Investigational New Drugs (HFB-230), Center for Biologics Evaluation and Research, 8800 Rockville Pike, Bethesda, MD 20892. For all other investigational drugs, the request for authorization should be directed to the Document Management and Reporting Branch (HFD-53), Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857.

D. Mechanism:
Before the use of the test article, the PI shall consult with the Vice President of Medical Affairs (VPMA) and the MHIRB Chairman concerning the intended use. In the absence of the VPMA, the PI shall consult with either the Medical Staff President or the Chief of the Medical Staff. In the absence of the MHIRB Chairman, the PI shall consult a physician member of the MHIRB. All parties must be in agreement as to the intended use of the test article.

Advanced or prospective MHIRB approval is not required. However, the MHIRB shall be notified by the PI in writing utilizing the MHIRB Emergency Use form, within 5 working days of use of the test article. Any subsequent use of the test article is subject to IRB review, although the FDA recognizes the possible need for the use of the test article on a second subject in a similar emergency situation. These procedures may be followed another time, however a full IRB review of the research protocol should occur at the next scheduled IRB meeting.

[21 CFR 56.102 (d), 21 CFR 56.104 (c), 45 CFR 46.102(i)]

Institutional procedures require that the MHIRB be notified prior to such use via consultation by the PI with the MHIRB Chairman; however, this notification should not be construed as IRB approval. Notification will be used by the MHIRB to initiate tracking to ensure that the investigator files a report within the five day time frame required by 21 CFR 56.104(c) and for future follow-up. The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, “interim,” “compassionate,” temporary” or other terms for an expedited approval process are not authorized. The IRB must either convene and give “full board” approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires “an IRB approval letter” before the test article will be shipped. If it is not possible to convene a quorum of the MHIRB within the time available, the IRB will send to the sponsor a written statement that the MHIRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not “IRB approval,” the acknowledgment letter may be acceptable to manufacturers and allow the shipment to proceed.

The Emergency Use episode will be assigned an MHIRB-EM number according to procedure. A MHIRB study file will be kept, but not kept with open, MHIRB approved research studies. One month after the utilization of the test article, the MHIRB will request a follow-up report from the PI regarding the outcome(s), any AE(s) or other pertinent information. The emergency use and follow-up will be reported to the MHIRB in a written report.

E. <u>Exception from Informed Consent Requirement</u>

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and *a physician who is not otherwise participating in the clinical investigation certify in writing* ***ALL*** *of the following* [21 CFR 50.23(a)]:

1. the subject is confronted by a life-threatening situation necessitating the use of the test article, **AND**
2. informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject, **AND**
3. time is not sufficient to obtain consent from the subject's legal representative, **AND**
4. no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator must make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the MHIRB within 5 working days after the use of the test article.

[21 CFR 50.23].

XI. EMERGENCY USE OF UNAPPROVED MEDICAL DEVICES

A. ***Definition:***

An unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 360(e)]. An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520(g) of the Act [21 U.S.C. 360 (j)(g)] and 21 CFR part 812.

The Food and Drug Administration (FDA) recognizes that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed.

B. Requirements for Emergency Use

All of the following conditions must exist to justify emergency use:

- the subject is in a life-threatening condition that needs immediate treatment, **AND**
- no generally acceptable alternative for treating the subject is available, **AND**
- because of the immediate need to use the device, there is not time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The physician may not conclude that an "emergency" exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends the physician may contact the Division of Emergency and Epidemiological Operations (1-301-443-1240).

FDA would expect the physician to follow as many subject protection procedures as possible, including obtaining:

- an independent assessment by an uninvolved physician;
- informed consent from the subject or a legal representative;
- authorization from the IDE holder, if an approved IDE for the device exists.

C. After-Use Procedures

After an unapproved device is used in an emergency, the physician must:

1. report the use of the device to the MHIRB within five days *[21 CFR 56.1049(c)]* and otherwise comply with provisions of the MHIRB regulations *[21 CFR part 56]*;
2. evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
3. if an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results. Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exists. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.

D. Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative **unless** both the investigator and *a physician who is not otherwise participating in the clinical investigation certify in writing* ***ALL*** *of the following [21 CFR 50.23(a)]*:

1)the subject is confronted by a life-threatening situation necessitating the use of the test article, **AND**
2)informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject, **AND**
3) time is not sufficient to obtain consent from the subject's legal representative, **AND**
4)no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the MHIRB within 5 working days after the use of the test article.

[21 CFR 50.23].

XII. REQUIREMENTF FOR HUD/HDE SUBMISSION

A. ***Definition:*** An HUD or humanitarian device is a device that is intended for the diagnosis or treatment of a disease or condition that affects fewer than 4,000 individuals in the US per year.

B. **Humanitarian Device Exemption (HDE) Approval process:**
An HDE must be filed with the FDA prior to use. Also, an HUD may only be used under the oversight of the MHIRB.

1. ***Initial MHIRB approval:*** The humanitarian use (HUD)device and its proposed use within the Methodist Healthcare must be reviewed and approved by the fully convened MHIRB. The following materials are required to be submitted for review:
   a. 17 copies of the following to the MHIRB Administration:
   b. The HUD manufacturer's product label, clinical brochure and/or other pertinent manufacturer information materials.
   c. A letter from MH purchasing indicating that the company is an approved MH vendor.
   d. The FDA HDE approval letter.
   e. A copy of the report from the independent certified public accountant verifying that the amount to be charged does not exceed the costs of research and development, fabrication and distribution for the device.
   f. Written notification from the Methodist Healthcare Finance Reimbursement Department that all reimbursement issues for the specific HUD are resolved.
   g. Written statements from the physician(s) responsible for the use of the HUD specifying for what clinical indication the device will be used, where it will be used, and by whom it will be used. The statements must contain information regarding the training of the physician who will be utilizing the HUD. The statements must also specify that use of the HUD will be limited to the clinical indication(s) listed in the FDA-approved product labeling.
   h. Written statements from the physician(s) responsible for the use of the HUD stating that there is no acceptable FDA approved device to treat the disease or condition for which the HUD will be used.

   Informed consent document - The MHIRB requires written informed consent for all investigative or non-FDA approved devices. The consent must contain the following items:

   1) A description of the HDE/HUD approval process:

   "Your medical care will involve the use of (specify device), which has been approved by the U.S. Food and Drug Administration (FDA) as a humanitarian use device (HUD). A HUD is a device used to diagnose or treat a disease or condition that affects fewer than 4,000 people in the United States each year. There is also no other device like the HUD that can treat this disease or condition. The FDA approves the clinical use of a HUD based on evidence that it does not pose a significant risk of injury to the patient. The FDA also believes that the potential benefit of

the device to the health of the patient outweighs the risks of its use. The FDA approval of a HUD is based on limited information that documents how effective this device is in humans."

2) A description of the HUD and how this device will be used in the clinical setting. It should be made very clear to the patient why he or she is a candidate for the use of this device.
3) A discussion of possible risks, side effects and/or adverse events associated with the HUD and its proposed clinical use.
4) A discussion of possible benefits associated with the clinical use of the HUD.
5) A discussion of any alternative treatments or procedures that the patient may wish to consider in lieu of clinical application of the HUD.
6) Voluntary consent statements and procedures should the patient wish to terminate use of the device.

***Note**: If the HUD is to be used in emergency situations which preclude obtaining informed consent prior to the use of the device, the physician is required to follow the MHIRB guidelines related to exception from informed consent. (See MHIRB Guidelines for details or contact the MHIRB Administration for assistance.)*

The physician must present a written plan detailing how patients or their legal representative will be informed of the use of the device in the event that prior informed consent is not obtained.

The physician submitting the HUD application must present the request at a fully convened MHIRB meeting. (The date and time of the meeting will be determined according to the submission date.) Upon review of the materials and the presentation by the physician, the MHIRB will vote to: 1) approve the use of the HUD, 2) disapprove the use of HUD or 3) table the use of the HUD until additional information is submitted.

The HUD and all associated reference materials will be assigned an MHIRB study number and documentation maintained according to MHIRB Guidelines and SOPs.

If approval is granted for use of the HUD, the submitting physician is then responsible for the following:

2. Continuation of IRB approval: If MHIRB approval is granted for the use of the HUD, the approval period will not exceed 12 months. Prior to the expiration of the approval the MHIRB will send a notice of reapproval. However, it is the physician's responsibility to seek reapproval. Failure to submit a reapproval application and obtain MHIRB reapproval will result in expiration of the MHIRB approval. If the MHIRB approval expires, all use of the device must cease.

For reapproval the following documents are required:

a) A cover letter, signed by the responsible physician(s), requesting continuation of MHIRB approval of the HUD. The cover letter should identify the HUD and describe how the clinical indications have been applied, where the device was used, by whom, and how many times the HUD was used.

b) A copy of the current FDA-approved product labeling for the HUD
c) For each patient in whom the HUD was used during the previous review cycle provide a summary of:
    1) the clinical indication for the use of the HUD
    2) any adverse events occurring in the patient and the relationship of the event to the HUD
    3) the medical record number of the patient
    4) the date the HUD was used
    5) the clinical outcome of the use of the HUD

3. ***Adverse Event Reporting:*** Any adverse event occurring with the use of the HUD must be reported within 5 working days to the MHIRB. The death of any patient receiving an HUD must be reported to the MHIRB within 24 hours. Contact the MHIRB Administration for the reporting form.

4. ***Modifications to the use of the HUD or the clinical use of the HUD:***
MHIRB approval is required for any modifications of the device and/or the proposed clinical use of the device. The following documents are required:
    a) a cover letter, signed by the responsible physician(s), describing the modifications to the device and/or the proposed clinical use of the device and the rational for such modifications.
    b) a copy of the HUD manufacturer's amendment to the HUD product labeling, clinical brochure, and/or other pertinent manufacturer informational materials corresponding to the requested modifications.
    c) a copy of the revised informed consent document

[21CFR814.112-126]

XIII. COOPERATIVE RESEARCH

Cooperative research projects are normally supported through grants, contracts, or other similar arrangements, and involve the grantee (or primary contractor) and other institutions. In such instances, the grantee remains responsible to the granting agency for safeguarding the rights and welfare of human research subjects. Cooperating institutions who conduct all or a portion of the research must comply with the same regulations (as though they received the funds directly) and may rely upon the review of another qualified IRB. MH will not undertake research based solely upon the reliance of another IRB's review action, including action of IRB's of federal agencies (NIH, FDA, etc.)

[21 CFR 56.105, 21 CFR 56.114, 45 CFR 46.114]

Outpatient Investigational Drug Studies Conducted or Continued on Hospitalized Patients:

Physicians may elect to conduct outpatient investigational drug studies in their office setting. These studies, if no MH facility is utilized, do not require MHIRB approval. However, should the patient become hospitalized during the course of the investigational drug therapy, the physician must abide by the Pharmacy policies governing the administration of such investigational drugs. The point of contact is the Pharmacy Coordinator for Investigational Drug Research.

Research Protocols From Other Institutions Continued on Hospitalized Patients at MH:

Patients on research protocols/studies from other accredited institutions may be continued on their investigational drugs. MHIRB review may not be necessary, but all questions should be referred to MHIRB Administration. The Pharmacy Coordinator for Investigational Drug Research is to be contacted for the procedure to follow.

XIV. ADVERTISING FOR RESEARCH SUBJECTS

The solicitation of research subjects by any form of advertisement is considered to be part of the informed consent process, and is therefore subject to full MHIRB review. Advertisements cannot be approved by the expedited process.

All advertisement for research subjects to be published in local newspapers, broadcast on television or radio networks, posted on the internet, posted or distributed in pamphlets or signs must be approved by the full MHIRB. All techniques, procedures, brochures, announcements, advertisements, promotional materials, financial rewards, enrollment fees, payment to subjects for participation, posters, subject stipends and any other plans, procedures or materials designed to enhance or induce enrollment of research subjects must be submitted in written form, to the MHIRB for full board approval.

Drafts of ads, brochures and printed material must be submitted along with a written plan of utilization and how any monetary rewards are to be administered. The proposed advertisements, along with an explanation of the type of media to be used and the frequency of use, must be submitted to the MHIRB for full review. Video and audiotapes used for recruitment/advertisement must be reviewed and approved by the MHIRB prior to implementation or utilization.

Initial submission of research protocols must identify the method(s) of recruitment of subjects. Any advertisements to be utilized should be included with the initial protocol application.

The following criteria will be used by the MHIRB to evaluate all proposed advertisements:

1. Is the advertisement in any way coercive? To any group? Is the intent population vulnerable and if so, does the advertisement unduly influence them?
2. Does the advertisement promise a certainty of cure beyond what is outlined in the consent and the protocol?
3. Does the advertisement promise or state an outcome or other benefit beyond what is in the consent and the protocol?
4. If the study involves a drug or device, does the advertisement imply or state that it is safe or effective?
5. If the study involves a drug or device, does the advertisement imply or state that it is equivalent or superior to any other drug or device?
6. Does the advertisement use terms such as “new treatment” or “new drug” without explaining that the test article is experimental?
7. Does the advertisement promise “free medical care” when the intent is to only state that the subjects will not be charged for taking part in the study?
8. Does the advertisement promote the payment in larger type or emphasize the payment participation?

If the answer to any of the questions above is yes, then the advertisement needs to be reworked before it can be approved for use with research subjects.

According to the FDA Information sheets, "advertisement to recruit subjects should be limited to the information the prospective subject needs to determine their eligibility and interest." If the following items are worded so not to violate any of the above issues (as identified in the above 8 questions) they may be included in the advertisement:

1. Name and address of clinical investigator and/or research facility
2. Condition under study and/or purpose of the research
3. In summary form, criteria that will be used to determine eligibility for the study
4. Brief list of participation benefits, if any
5. Time or other commitment required of the subjects
6. Location of research and person or office to contact for further information

A reviewer will complete the advertisement checklist and attach to the proposed advertisement, which will be placed in the MHIRB study file.

Following a decision by the MHIRB regarding the advertisement, the PI will be notified in writing of the decision.

Any change to the advertisement must be submitted to the MHIRB for review and approval prior to implementation of the change.

[CFR 21 312.7 (a); CFR 812.7); 21CFR50.20;1998 FDA information Sheets]

XV. STUDY STATUS and CLASSIFICATION

A. ***Status:***

1. *Active/Open:* A research project is considered active/open if any of the following conditions apply:
   - research plan is active and currently enrolling subjects
   - enrollment is closed but subjects continue to be followed or statistical analysis is being completed
   - project is put on hold by the PI, sponsor or MHIRB whereby enrollment and/or activities of the research plan are on hold
2. *Closed:*

   A research project is considered closed if any of the following conditions apply:
   - completion of project - when study objectives are met and all aspects of the research plan are completed. The MHIRB should be notified of study closure within three months of the closure. IRB Project Review Form, including a report of subject experiences, must be submitted to the MHIRB
   - project never initiated at local site - when for whatever reason, the project is never opened, nor subjects enrolled at MH.
   - termination by MHIRB - when the MHIRB closes the study due to concerns for the safety and welfare of research subjects, the integrity of the project; or failure of the PI to obtain reapproval of project. The MHIRB will notify the FDA in these instances.
   - closed by the sponsor - when for whatever reason the sponsor closes all aspects of the study

   Once a study is closed with the MHIRB, the study cannot be reopened. A new research proposal must be filed with the MHIRB and the process followed for submission of a new research proposal.

   [21 CFR 56.108(a) 21 CFR 56.113]

B. ***Definitions of subject status:***

- *Total number enrolled at MH* - all subjects who signed informed consents at MH since the inception of the study
- *Subjects signing ICF* - any human subject or subject's legal representative who signed a consent, regardless of the length of time the subject participated in the study or whether actual study procedures were performed
- *Subjects active* - all subjects who are currently, at the time of the report, are participating in any study activities, including follow-up activities
- *Subjects completing study* - all subjects who have completed all aspects of the study, including follow-up visits, telephone contacts, etc.
- *Subjects withdrawn* - all subjects who, after signing the informed consent, were withdrawn by the PI or sponsor, who requested to be withdrawn or failed the screening
- *Subjects lost to follow-up* - all subjects who, after signing the informed consent, cannot be located and will therefore not be participating in further activities of the study
- *Enrolled since last review* - number of subjects a MH who signed ICF since last review cycle report filed with MHIRB

C. *Classification:*

Research studies submitted for MHIRB review may be classified as:

- Drug/biological agent: any chemical compound or substance intended to be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation or prevention of disease or other abnormal condition;
- Medical device: a diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body;
- Non-drug, non-device: any study that does not involve a drug, biologic agent or device; examples include medical record review/research; diagnostic data review, genetic predisposition/risk studies; psychological studies, or any study not fitting the definition of drug/biologic agent or device, etc.
- Phase I, II, III, IV study:
  --Phase I - trial using healthy volunteers to look at safety and tolerance of the product
  --Phase II - uses subjects with targeted disorders to look at safety and preliminary efficacy; establishes a dosing regimen
  --Phase III - uses subjects with targeted disorders to look at overall safety and efficacy; uses large numbers of subjects
  --Phase IV - post-marketing studies to delineate additional information about the risk, benefit and optimal use

Studies classified as medical records research and genetic studies are subject to additional procedures as outlined below:

D. *<u>Medical Record Research:</u>*

According to the Tennessee law, medical records do not constitute public records and therefore the information contained within the medical records is considered confidential. The Tennessee Code Ann. § 63-2-101(b)(1) and (2) allow disclosure of patient-identifying information for:

1) statutory required reporting to health or government authorities;
2) the third party payors such as insurance companies for the purpose of utilization review, case management, peer reviews or other administrative function; and
3) pursuant to a subpoena issued by a court of competent jurisdiction

The Patient's Privacy Act grants patients a statutory right to privacy for care received at a hospital or clinic [Tenn. Code Ann. § 68-11-1502] and prohibits disclosure of name, address and other identifying information of a patient.

The role of the MHIRB is to protect the rights of human subjects. Strict federal criteria, including an informed consent document, are used to allow a person/agency to collect data on human subjects. To ensure that these criteria are followed, whenever an

individual/agency requests medical records or patient lists for "data" collection or for a "project" or "research" the individual responsible for the project must submit the request in writing to the MHIRB Administration utilizing the Medical Record Research Request form.

The MHIRB Administration will make a determination as to whether the request represents research. If the request does not represent research, the form will be completed by the MHIRB Administration, given back to the individual proposing the project, who is responsible for taking it to HIM in order to request and receive the desired medical records. The MHIRB will also forward a copy of the completed form to the HIM Director.

If the MHIRB Administration determines that the proposed project represents research, the individual proposing the project will be instructed as to how to submit the project for MHIRB review. Once the project has been reviewed by the MHIRB, the appropriate portion of the form will be completed and given to the individual. If the MHIRB disapproves or approves the project, the action will be noted on the form. If the project is approved, the individual must present the form to HIM in order to request and receive the desired medical records. If the project is disapproved by the MHIRB, the individual may not have access to medical records. After MHIRB review and decision, the MHIRB will forward a copy of the completed form to the HIM Director.

E. *Genetic Research Studies:*

If a proposed study involves the collection of tissue/blood/specimens for genetic purposes the ***MH System Policy S-06-014*** (outlined below) applies and governs the submission and application of the research for review:

Purpose: To clarify the ownership of donated tissue, specimens, and/or derivatives including immortalized cell line and provide direction for Methodist Healthcare participation in research protocols utilizing donated samples.

Policy: Gene study research involves the analysis/investigation of biological materials including human DNA and RNA for the purposes of developing new scientific tests and treatments. Such purposes include predicting risk of disease, identifying carriers and establishing clinical diagnosis and prognosis.

Methodist Healthcare shall be in compliance with its governing Board of Directors and Trustees by adhering to the Discipline of the United Methodist Church and its standards regarding genetic research. Book of Discipline, United Methodist Church, p. 95-96

Procedure:

1. Tissue and specimen samples are collected from patients during diagnostic and surgical procedures.
2. A patient must have full knowledge of the research objectives and discuss the proposal with his/her physician. If agreeable to participation, the patient will give "informed consent" to each element of the research protocol.
3. A patient who donates material for research does so freely and with no coercion. Identifiable samples and derivatives including, but not limited to

immortalized cell line will not be sold or used as a profit-making venture for the patient of Methodist Healthcare or any other third party. Informed consent for any study must be obtained whenever the specimen can be linked to the subject from which it came. Gene studies can greatly impact the subject and his/her heirs, therefore informed consent must be obtained for every part of research for which the specimen is used. Should a stored specimen, which is identifiable to a particular individual, be requested for research, the patient or the next-of-kin shall be approached for permission to use the sample for research purposes. If there is no person to assume responsibility for the specimen, it will not be used.

4. Confidentiality will be maintained through all steps of the research project. Specifics are to be submitted for IRB approval to maintain strict standards for protecting the privacy of the patient. Should potentially life-threatening or life altering information be learned from the research project, the patient or next-of-kin should be informed of the findings. It is then the patient's or next-of-kin's responsibility to act on the information by consulting his/her physician.

5. If a specimen does not meet research requirements, the sample cannot be used for other research projects without informed consent by the patient. Samples in laboratory storage at Methodist Healthcare facilities are owned and maintained by the facility and will be subject to the criteria established above.

XVI. INFORMED CONSENT

A. Definition:

Informed consent is a process whereby the PI provides the human subject with information, in written, verbal, visual or other form, about the intended research. The subject is then given ample opportunity to ask questions, seek clarification, request additional information prior to agreeing to voluntarily participate in the research. The subject and investigator signify that consent was obtained from the subject by signing the informed consent document that has been approved by the MHIRB. The informed consent process begins with the recruitment of subjects and continues throughout the duration of the research. Only MHIRB approved informed consent documents can be used when obtaining consent from the subject. This approval is indicated by an MHIRB stamp on each page of the informed consent document. The approval stamp includes the date approved.

B. Process:

Research-related procedures, including screening procedures, may not begin on any potential research subject unless legally effective informed consent has been obtained from the subject or their legally authorized representative. The purpose of informed consent is to ensure that potential volunteers are informed about the possible risks and benefits of the study so that they may make an informed decision regarding participation in the research.

No informed consent, either oral or written, may be coercive or unduly influence the subject. Informed consent may not involve exculpatory language, through which the subject waives, or appears to waive, any of their legal rights, including the release of the investigator, institution, sponsor or its agents from liability due to negligence.

The PI, Co-PI may designate one or more individuals who are trained and qualified to obtain consent from the potential subject. The individuals must have documented credential verification through the MH Medical Staff Office. Only the PI, Co-PI or individuals identified to the MHIRB may obtain consent.

The PI is 100% responsible for all aspects of the consent process, for ensuring that consent is obtained prior to the initiation of any screening or study related procedures and for the maintenance of the consents. This accountability and responsibility cannot be delegated.

C. FDA Requirements:

The FDA requires that specific information regarding the research project be provided to each potential subject and include:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including the identification of any procedures that are experimental.
5. A description of reasonably foreseeable risks or discomforts to the subject.
6. A description of any benefits to the subject or others that may reasonably be expected from the research.

7. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
8. A statement describing the extent to which confidentiality of records will be maintained. It should also be noted that the FDA may inspect the records.
9. An explanation as to whether compensation is available.
10. An explanation as to whether any medical treatments are available if injury occurs, and if so, what they consist of and where further information may be obtained.
11. Whom to contact for questions about the research and the rights of research subjects.
12. Whom to contact if there is research-related injury.
13. A statement that participation is voluntary, and that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
14. A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which they are otherwise entitled.

In addition, when appropriate, the following elements should be provided to the subject in the informed consent:

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

Note that these 6 elements are not required by the FDA for inclusion in the informed consent document, but are a requirement by the MHIRB.

D. ***Methodist Healthcare Requirements:***

1. A consent form shall be developed for the research study in accordance with 21CFR50.25 and maintained for each subject. MHIRB requires all basic and additional elements of informed consent as delineated in 21CFR50.25, unless deemed inappropriate or waived by the MHIRB.
2. The MHIRB approved consent form must be stamped with the MHIRB approval seal and date. Only this form may be photocopied and used to obtain subject consent. Consent forms that do not have the MHIRB approval stamp on them may not be used.
3. All consent forms must be approved by the MHIRB, and signed by the subject or the subject's legally authorized representative, witness and PI.
4. A copy of the informed consent form must be given to the subject or the subject's legal representative signing the form. One copy is to be placed in the subject's medical record and will become a permanent part of the subject's medical record.
5. Informed consent must be obtained in person unless criteria for telephone consent applies. Informed consent documents cannot be mailed to potential subjects to obtain a signature. Consent documents can be mailed to potential subjects or

subject's legal representative to provide information. The signature page is to be crossed out with a notation indicating that signature must be obtained in person.

6. A 'short form' written consent stating the elements of informed consent as outlined above may be orally presented to the subject or their legally authorized representative. However, a written summary of what is to be said must be approved by the MHIRB. The short form is to be signed by the subject or their legal representative, and they are to receive a copy of the short form and the written summary. The person obtaining the consent must sign the written summary. There must be a witness to the entire oral presentation, who is provided with the written summary. The witness shall sign both the short form and the written summary.
7. The name of the institution shall appear on the top of the consent form.
8. The entire title exactly as shown on the research protocol shall be on page one of the consent form.
9. The PI will be listed on the consent form, along with his/her phone number.
10. There shall be a space for subject initials on each page of the informed consent form.
11. The MHIRB consent template must be utilized to construct the consent document.
12. The PI must disclose in the written informed consent document any conflicts of interest and any financial gains to be seen from the research.
13. All HIPAA required language must be included in each consent. (See consent template for exact wording.

A signed copy of the informed consent document will be given to the subject or their legally authorized representative and a copy placed in the subject's medical record and a copy retained for the PI's research study file.

The PI must provide the MHIRB with a complete list, by name, of those individuals who will be obtaining consent, along with their telephone numbers. It is the PI's responsibility to ensure that only individuals who are qualified and competent may obtain consent. The MHIRB reserves the right to review the qualifications of those individuals designated to obtain consent and to stipulate those qualifications.

Questions related to the status and capability of an individual to provide consent for a subject should be clarified with MHIRB and/or Legal Affairs.

Guidelines for the preparation of informed consent forms and an example of an informed consent form may be found in the Appendices.

Short form written consent:
A short form written document can only be utilized with the approval of the MHIRB. In the event the PI desires to use a short form, prior MHIRB approval of the form is required and the form must adhere to 21CFR50.27(b)(2).

[21 CFR 50.20, 21 CFR 50.25, 21 CFR 50.27, 45 CFR 46.109 (b) (c), 45 CFR 46.116,45 CFR 46.117]

E. Telephone Consent For Research Protocols

1. Telephone consent should only be considered if:
   (a) management of the medical condition is an urgent concern and the participant is unable to give direct consent for the investigation.
   (b) the potential participant is unable to give informed consent because the subject is a minor or impaired in mental capacity or consciousness and the investigation is ethically appropriate.
   (c) the risk of the investigation is minimal and the potential benefit is equivalent or greater than the standard care.

2. Telephone consent process to be documented:
   (a) why a written consent is not obtainable
   (b) the person obtaining the consent, their address and telephone number
   (c) the person giving the consent and their legal relationship to the subject. The person contacted should be the person who is empowered by law or the one traditionally utilized in providing consent. For example, the legal guardian, an appointed power of attorney, or a spouse would be appropriate. The investigator should establish some means of assuring himself/herself that the person is the subject's legal guardian or next of kin, particularly in situations where the investigator does not have a well established relationship with the subject and family members.
   (d) the context of the discussion
   (e) responses/comments of the person giving the consent.
   (f) the witnesses to the consent process. MH System Policy requires 2 witnesses and their signatures on all telephone consents.
   (g) date and time of the informed consent process.

After obtaining telephone consent, then a complete copy of the informed consent document should be mailed or given to the person providing consent in a reasonably expedient manner (within 24 hours). The signature page should be crossed out with a notation indicating that telephone consent was obtained, the person obtaining consent, the person providing consent, date, time and witness.

In circumstances where the enrolled subject is temporarily unable to give informed consent and telephone consent is obtained but the subject later recovers, the subject should then be given information concerning the study and informed consent sought from the subject for continuing in the investigation. The subject's wishes concerning participation in the study should be honored.

F. Consent From Potential Subjects With Altered Mental Status:

Potential subjects whose mental status renders them incapable of making a decision regarding their own care and well-being may not be enrolled in a research study unless there is a legally authorized representative who can act on behalf of the subject.

Subjects who are enrolled in a research study and whose mental status changes and they request to be removed from a research study should be removed from the study.

Enrollment in a research study or signing of an informed consent document must adhere to legal standards and guidelines of Methodist Healthcare. Questions about or

assistance with the informed consent process should be referred to the MHIRB Administration. MH legal affairs assistance may also be sought.

G. Consent From Illiterate English Speaking Subjects:

Potential subjects who are mentally competent and understand English, but do not read or write English or are physically disabled, may be enrolled in research studies by "making or placing an X" on the consent document in the space for the participant signature after the study information has been reviewed with them. An impartial witness is to be present to attest to the adequacy of the consent process and the subject's voluntary participation.

The individual obtaining the consent and the witness must sign the consent document in addition to the subject.

Upon verbal explanation, the potential subject should be able to:

1) understand the concepts of the study
2) understand the risk(s) and benefit(s) of being in the study
3) indicate approval or disapproval to enter the study

The person obtaining the consent should ascertain the above and document the method(s) utilized to communicate with the subject and the method(s) utilized by the subject to communicate agreement to enter the study.

A signed copy of the informed consent document shall be given to the subject or their legally authorized representative.

Video and audiotaping of the process may be utilized with permission of the individual.

Note: MH system policies regarding video and audiotaping must be followed.

Questions about or assistance with the informed consent process should be referred to the MHIRB Administration.

[21CFR50.27(b)]

H. Consent From Non-English Speaking Subjects:

Non-English speaking individuals may be included in research and should not be excluded solely upon the basis of language.

Anticipated non-English speaking subjects:

If it is anticipated that the population for a research study will include non-English speaking subjects, the informed consent document should be provided in a language understandable to the subject or their legally authorized representative. The non-English informed consent document must be approved by the MHIRB.

The PI must have a translation of the non-English informed consent document prepared (preferably by a native speaking translator) and presented to the MHIRB to assure the accuracy of the document. The person obtaining consent must ensure that the subject's questions are answered which may necessitate the use of a translator.

It is not acceptable for a verbal translation of an English informed consent document to be substituted for a written translation.

A short version of the informed consent document is not acceptable.

The translator, if utilized, individual obtaining consent, subject and witness must sign the document.

After the informed consent has been obtained, the subject or their legally authorized representative will be given a copy of the signed informed consent document.

Unexpected encounter with non-English speaking subject:
In the event a non-English speaking subject is unexpectedly encountered and there is not a written translation of the informed consent document, an oral translation may be utilized. The language line service for MH is the Certified Languages International (1-800-237-8434) and the Patient Affairs Department may be contacted for assistance in accessing this service to assist in translations. The PI must carefully consider the risks associated with the research study and whether the non-English speaking subject fully comprehends or there is a language barrier. Failure to fully inform the subject or satisfactorily answer all the subject's questions may render the signature on the consent illegal and certainly constitutes an ethical dilemma.

If a translator is utilized during the informed consent process, the proceedings should be documented in a language understood by the subject and signed by the translator, witness and subject.

The subject will be given a copy of the signed short form.

Questions about or assistance with the informed consent process should be referred to the MHIRB Administration

I . Exception from informed consent:

21CFR50.24 allows the MHIRB to approve research without requiring that informed consent of all research subjects be obtained if the IRB with the concurrence of a licensed physician who is a member of or consultant to the MHIRB and is not participating in the research

A. documents:
    1) subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions
    2) obtaining informed consent is not feasible because:
        - medical condition precludes consent
        - there is no time to get consent from legally authorized representative
        - prospective identity of likely subjects not reasonable

3) prospect of direct benefits to study subjects because:
    - life-threatening situation that necessitates treatment
    - data support potential for direct benefit to individual subjects
    - risk/benefit of both standard and proposed treatments reasonable

4) waiver needed to carry out study

5) plan that defines therapeutic window during which investigator will seek consent; Plan must ensure that PI will attempt to obtain consent and document such efforts; documentation will be provided to MHIRB upon request and at time of continuing review.

6) review and approval of consent and family objection procedures

7) provisions of additional protections including, but not limited to:
    - consultation with community representatives
    - public disclosure of plans, risks, benefits and study results
    - establishment of independent DSMB

B. reviews planned procedures and results of attempts to inform the subject or the subject's legally authorized representative, at the earliest possible opportunity, of inclusion in the research. In the event of the subject's death, the PI should make every attempt to disclose to the subject's family the subject's enrollment in the research.

C. ensures that a separate IND or IDE is acquired regardless of presence of previous IND or IDE.

The MHIRB will document that the research meets the requirements as delineated in 21CFR50.24. If the MHIRB determines that the study does not meet 21CFR50.24, the MHIRB will promptly notify the PI and the sponsor in writing of its determination and rationale. The MHIRB will notify the PI and the sponsor of all information publicly disclosed.

[21CFR50.24; 21CFR56.109]

XVII. CONSIDERATIONS FOR VULNERABLE POPULATIONS IN RESEARCH

At the time of initial submission of a research study to the MHIRB, the PI must indicate the intent to include any vulnerable populations in the research study. If any vulnerable populations are to be included, the research plan must detail the protections afforded those individuals specifically outlining the risks and benefits. Details for vulnerable populations in research are detailed in 45CFR46 Subparts B,C and D. Research studies considered for review by MHIRB and involving vulnerable populations will be reviewed under the regulations in 45CFR46 with consultation from experts in the area of investigation.

CHILDREN in RESEARCH:

Pediatric only research protocols, not involving an adult population will be reviewed by the University of Tennessee IRB as provided in the FederalWide Assurance agreement between the University of Tennessee and Methodist Healthcare. The UTIRB will be the IRB of record and all research conducted with MH pediatric facilities must adhere to the UTIRB requirements and be approved by the Le Bonheur Research Committee. (Guidelines for the UTIRB and the Le Bonheur Research Committee may be obtained from these entities). Representatives from the MHIRB are members of the Le Bonheur Research Committee. However, primarily adult research protocols with a pediatric component that will be reviewed by the MHIRB.

The specific MHIRB requirements for involving children in research at MH are detailed below. .

A. Definition:

1. **"ASSENT"** means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as consent. [45 CFR 46.202(b)]

2. **"Children"** are persons who have not attained the legal age for consent to treatments **or procedures** involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In Tennessee, children less than 18 years of age are considered to be "minors" and therefore are a 'vulnerable' population. [45 CFR 46.202(a)]

   Additional definitions, such as guardian, parent, will be adhered to as defined in the Tennessee law. Legal counsel will be sought to assist in making any determinations regarding the status of the child or adult representing the child prior to approval for enrollment in research whenever there is indication.

   According to FDA guidelines, minors are considered to be a vulnerable population, and special safeguards to ensure that their rights and welfare are protected must be included in the research plan and approved by the MHIRB.

B. The MHIRB will seek assistance/consultation from pediatric experts when reviewing or considering for review research involving children. The MHIRB will consider the following factors when children are the subject of research studies:

1. Data available from previous pre-clinical and clinical trials.
2. Risk versus potential benefit ratio. The MHIRB shall determine which of the following risk categories the proposed research study applies to.
   (a) Research not involving greater than minimal risk
   The IRB must find that the consent of one parent, and the assent of the child will be obtained.
   (b) Research involving greater than minimal risk but presenting the prospect of direct benefit to the subject
   The IRB must find that the:
      i) risk is justified by the anticipated benefit
      ii) relation of benefit to risk is at least as favorable to the subjects as that presented by alternative approaches.
      iii) consent of one parent or guardian, and the assent of the child
   (c) Research involving greater than minimal risk, no prospect of direct benefit to the subject, but likely to yield generalizable knowledge about the subject's condition or disorder
   The IRB must find that the:
      i) risk represents a minor increase over minimal risk
      ii) intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations.
      iii) intervention or procedure is likely to yield generalizable knowledge about the subject's disease or condition that is of vital importance for understanding or ameliorating the disease or condition.
      iv) consent of both parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the minor child. Assent of the child is to be obtained.
3. Protection of the privacy of the children and their parents/guardians.

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, the special ethical and regulatory considerations in 45CRF46, Subpart D (Additional DHHS Protections for Children Involved as Subjects in Research) will be enforced.

Research that is contrary to the rights and welfare of child-subjects is prohibited.

All research involving children regardless of risk must be submitted for review by the Full MH IRB review.

When children or minors are involved in research, the regulations require the **assent** of the child or minor and the **permission** of the parent(s) or legally authorized representatives, in place of the consent of the subjects. While children may be legally incapable of giving

informed consent, they nevertheless may possess the ability to **assent** to or dissent from participation. Out of respect for children as developing persons children should be asked whether or not they wish to participate in research, particularly if the research: (1) does not involve interventions likely to be of benefit to the subjects; and (2) the children can comprehend and appreciate what it means to be a volunteer for the benefit of others.

C. A minor's participation in research projects may occur after legally effective informed consent of the subject's legally authorized representative is obtained. The assent of the child should be sought in situations in which the child has sufficient intellectual and emotional ability to comprehend the concepts involved. The table below serves as a general guideline:

Age (years)	**Forms Required**	**Way minor is addressed in the consent form**	**Who Signs**
0-6	Consent Form	Your child	Parent signs consent
7-11	Consent Form	Your child	Parent signs consent
	Assent Form	You	Minor signs IF they understand what is happening
12-17	Consent Form	Your child	Parent signs consent
	Assent Form	You	Minor signs assent

- It is recognized that there are special instances in which the child in the particular age group is not capable of understanding the concepts involved. In those rare cases, assent is not a necessary prerequisite for proceeding with the research, although the rationale for not requesting assent must be outlined in study records.
- If the test article holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of research, requesting assent from the child is not a prerequisite for proceeding with the research.
- Younger children are not required to sign the assent form. However a witness must sign that the child granted assent.

Should an assent form be utilized, the HIPAA authorization will be constructed as a separate documents per MH Legal Department stipulations and guidelines.

[45 CFR 46.405; 45 CFR 46.406; 45 CFR 46.407; 45 CFR 46.408] Tennessee Statutes

XVIII. PAYMENT TO RESEARCH SUBJECTS

The MHIRB will determine that the risks to subjects are reasonable in relation to the anticipated benefit. *[21 CFR 50.25 (a) (3)]*. With regard to payment to subjects, the goal is to insure that the subject's participation is voluntary, and that the subject is able to make an informed choice based upon the risks and benefits of participation and not on financial incentives. Each protocol will be considered individually to assess the risk and benefits to the participant.

Payment for Participation:
The MHIRB will review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. *[21 CFR 50.20]* The amount and method of payment, as well as the schedule of payment should be presented to the MHIRB at the time of initial review of the study.

With regard to the payment amount, there is no specific dollar amount which can be definitively approved/disapproved in advance. Each proposed payment will be evaluated on a case by case basis and considered in light of all the facts and circumstances of the research project. Subjects should be paid enough to offset any inconvenience, or time spent on the study, but not so much that their decision to participate is influenced by the amount offered. There should be some benefit to the subject, other than financial, for participation in any study that involves a great deal of hardship or pain.

In evaluating the appropriateness of the dollar amount and the type of payment (lump sum vs. hourly payment), the MHIRB will consider the risk involved, the degree of inconvenience, difficulty, pain etc., as well as any benefit, if any, the subject may receive from participation. Both lump sum payments and hourly payments are allowable depending upon the circumstance. Obviously hourly payments would be appropriate for filling out a questionnaire but not for undergoing a biopsy.

Reimbursement:
Subjects may be reimbursed for any reasonable out of pocket amounts expended for participation in the study (parking, transportation, etc.).

Timing of Payment:
Any credit or payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Withholding payment until the subject has completed every procedure or visit in a long, multi visit study may appear coercive. For studies which extend several weeks or longer, payment should be prorated based on the amount of time subjects have spent participating.

A small proportion as incentive for completion of a study is acceptable to the FDA, provided that such incentive is not coercive. The MHIRB will determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would have otherwise withdrawn.

Informed Consent Disclosure:
All information concerning payment, including the amount, the method, the schedule of payment (s), should be set forth in the informed consent. Regardless of how payment is calculated (hourly, per visit, etc.) the informed consent should clearly state the maximum amount of payment available.

Explanation should be provided as to how subjects may receive payments that allow subjects to remain anonymous. Subjects should be advised if they are required to provide social security numbers or other confidential information, as well as advised if the payment is more than six hundred dollars ($600) in a calendar year that it must be reported as income to the IRS.

[21 CFR 50.25 (a)(3), 21 CFR 20]

XIX. INVESTIGATOR RESPONSIBILITIES and QUALITIFACTIONS

A. Qualifications:

Individuals who conduct research must have the appropriate credentials to carry out all aspects of the study in order to ensure the research subject's safety. Investigators are classified as physicians or non-physicians. Non-physician investigators are further classified as Associates of Methodist Healthcare or non-associates. The Methodist Healthcare Medical Staff Services provides verification of credentials prior to the initiation of research at MH. The MHIRB Administrative staff will verify with the Medical Staff Services the credentials of all investigators prior to presentation of the research study to the MHIRB for review. Potential investigators who have not completed the credential process at MH or whose credentials cannot be verified will not be allowed to submit research for MHIRB review nor allowed to conduct research at MH until credentials are verified and accepted.

All interventional research studies are required to have as PI a MH physician staff member. Residents are not allowed to be PI of an interventional or diagnostic research study.

All investigators (PI and Co-PI) must complete a new investigator profile and submit it along with a current CV to the MHIRB at the time of the first MHIRB study submission. It is the responsibility of the PI and Co-PI to submit updated CV whenever changes occur.

The investigator is responsible for obtaining human subject protection training as indicated by the MHIRB.

B. Responsibilities:

Investigators who conduct research under the auspices of MH agree to adhere to the ethical principles regarding research in human subjects as set forth in the Code of Federal Regulations, the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research, the Belmont Report, the Nuremberg Code* and by MH policies and procedures governing research. Both investigators and the institution are bound by federal guidelines regarding the use of human subjects in research.

All investigators and their associated research staff are expected to conduct themselves in a professional manner with respect for the subject and to protect the welfare and safety of the subjects at all times. All studies are expected to be carried out with integrity and in a scientifically valid manner. Any suspicion of scientific misconduct will be investigated according to MH System Policies.General responsibilities of investigators are outlined in the FDA form 1572, the Code of Federal Regulations and the Statement of Investigators by device companies. The investigator is directed to the MHIRB guidelines for additional information. Questions may be directed to MHIRB Administration at 901-726-2323.

First time investigators are required to meet with the MHIRB Administrative staff and review the investigator responsibilities prior to the acceptance of a new reserch study. The PI will indicate agreement to follow the MHIRB guidelines for conducting by the study by signing the investigator responsibility agreement.

Investigators conducting research at MH are expected to adhere to the following guidelines:

1. **Research Study Submission:**
   In accordance with MHIRB guidelines, the investigator will submit under his/her original signature a research study and any supporting documentation important to the project. The study materials/protocol submitted for MHIRB will include (but are not limited to):
   - accurate title of research study with consistency throughout the materials
   - purpose of the study and expected benefits
   - IND/IDE number and documentation or justification and documentation from the FDA that an IND/IDE is not needed
   - sponsor of the study
   - results of previous related research and references
   - subject inclusion/exclusion criteria
   - justification of vulnerable populations to be included along with measures to protect the population
   - study design including data collection tools, procedures to be performed, management of adverse events,
   - investigator's brochure
   - identification of the laboratory to be utilized and evidence of the lab's certificationn/licensure to conduct the tests; If the FDA 1572 form is utilized, the PI must identify the laboratory to be utilized
   - informed consent document along with procedure for obtaining consent; in the event of minors or vulnerable populations documentation and informed consent documents must included and details provided regarding how protection will be provided
   - compensation to research subject for participation or injury sustained as result of study
   - extra costs to subjects and/or the subject's insurance associated with participation in the study
   - provisions for protection of subject's privacy and confidentiality measures
   - advertisements/incentives
   - documentation from previous/other IRB reviews, agencies or institutions, FDA audits or other documents that may influence the outcome of the MHIRB review

2. **Disclosure:**
   The PI must disclose to the MHIRB at the time of each new study submission, all conflicts of interest, including but not limited to financial, personal or professional conflicts. The PI is accountable for notifying the MHIRB of any change in financial, personal or professional status change of the PI or research staff after the initial disclosure.

3. Informed Consent:

The investigator must obtain informed consent from each subject, or the subject's legally authorized representative, before study related procedures may begin. Informed consent must be obtained using the MHIRB approved informed consent form. Only informed consent forms that have been stamped with the MHIRB seal of approval may be used to obtain consent (photocopies of the MHIRB approved form must be used). Obtaining consent is the responsibility of the PI. The PI may delegate this task, provided this is a formally defined task to a person who has received appropriate training and instruction; however, the PI retains 100% accountability and responsibility.

The investigator must provide the MHIRB with a list of all individuals authorized by the PI, qualified and trained to obtain informed consent along with their telephone numbers. Verification of credentials by the MH Medical Staff Office is required for all individuals who will be obtaining consent. The MHIRB reserves the right to approve or disapprove of any individual to obtain consent on any study.

4. Research Oversight:

The PI is 100% accountable for all activities related or involved in the conduct of the research study and for the actions of all the research team members. Only duly authorized research team members may enroll a subject in a research study.

The payment of a "finder's fee" to a member of the MH hospital staff is considered inappropriate and unethical. Fees may be paid to an individual as compensation for the proper, ethical and professional enrollment of a research subject into a clinical trial. Administration of fee arrangements rests with the PI, but with full approval of the appropriate program director and the MHIRB. Questions regarding differences between finder's and enrollment fees should be directed to the Chairman of the MHIRB prior to the dispensing of any money.

5. Research Study Revisions:

The PI must submit proposed research project changes in the study protocol or consent form for review and approval by the MHIRB before the change is implemented. A copy of the protocol amendment or changes, two copies of the modified consent form, a completed Revision/Amendment for Research form and sponsor documentation, must be submitted to MHIRB Administration. One copy of the modified consent should have the changes highlighted. The second copy of the modified consent will be stamped if approved by the MHIRB.

Revisions require the original signature of the PI and the Co-PI.

In cases in which the change will eliminate or reduce immediate hazards to the subject, the change may be implemented prior to MHIRB approval following CFR guidelines. However, the change must be reported to the MHIRB within five working days. The MHIRB may, following review, vote to approve or deny approval of the change.

6. Adverse Events:

The investigator will report to the MHIRB any:

1. *Adverse event:* an undesirable, an unintended, although not necessarily unexpected result of therapy or other intervention .

and

2. *Serious adverse event:* incident/episode when the subject outcome:
   a. *results in death
   b. *is life-threatening or places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred
   c. *results in a persistent or significant disability/incapacity (substantial disruption of one' ability to conduct normal life functions
   d. *results in or prolongs an existing subject hospitalization (an overnight stay in the hospital, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation)
   e. *is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis)
   f. is a cancer
   g. is the results of an overdose whether accidental or intentional
   h. other medical events that may result not in death, not be life-threatening or not require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the starred (*) outcomes listed previously.

Adverse Event Reporting:

A written report for **non-serious adverse events** must be filed, with the PI's original signature, with the MHIRB Administration within 5 working days of discovery using the MHIRB Adverse Event Report Form. Follow-up reports regarding the incident must promptly be reported to the MHIRB. The PI should use his/her judgement when determining whether an untoward event is reportable. However, the MHIRB encourages reporting all adverse events to the MHIRB regardless of the requirements of the sponsor.

All **serious adverse events** (life-threatening events that may or may not be due to the test article), and all fatal events, regardless of the relationship to the test article, must be reported to the MHIRB (written/e-mail/fax is acceptable) within 72 hours of their occurrence. In the event that email or fax is utilized for the initial reporting of the serious adverse event, the original report, under the PI's signature, should be immediately sent to the MHIRB.

Upon receipt of all adverse events occurring at MH, the MHIRB Administration will send the report to the MHIRB Chairman for immediate review. The Chairman may require more information prior to reporting to the full MHIRB. The Chairman may also immediately suspend the research project or take action to protect the immediate welfare of the research subjects. The adverse event and any follow-up action(s) by the Chairman will be reported at the next available MHIRB meeting.

The MHIRB will review the incident, and may require changes to the informed consent document, study procedures, suspend some or all study-related procedures pending the completion of MHIRB review or permanently terminate MHIRB project approval based upon an increased risk to the subject. The investigator may be required to submit additional information or reporting as deemed appropriate or necessary by the MHIRB.

7. Safety Reports:

In the case of multicenter studies using an investigational drug or device, it is understood that the investigator will be receiving from the sponsor safety reports sent to the FDA from all centers participating in any study involving that drug or device. The investigator, under his/her original signature is expected to promptly forward these reports to the MHIRB using the Safety Reports Form.

8. Advertisements and Inducements for Research Subjects:

The solicitation of research subjects by any form of advertisement is considered to be part of the informed consent process, and is therefore subject to full MHIRB review. Advertisements cannot be approved by the expedited process or by administrative approval

All advertisement for research subjects to be published in local newspapers, broadcast on television or radio networks, posted on the internet, posted or distributed in pamphlets or signs must be approved by the full MHIRB. All techniques, procedures, brochures, announcements, advertisements, promotional materials, financial rewards, enrollment fees, payment to subjects for participation, posters, subject stipends and any other plans, procedures or materials designed to enhance or induce enrollment of research subjects must be submitted in written form, to the MHIRB for full board approval.

Drafts of ads, brochures and printed material must be submitted along with a written plan of utilization and how any monetary rewards are to be administered. The proposed advertisements, along with an explanation of the type of media to be used and the frequency of use, must be submitted to the MHIRB for full review. Video and audiotapes used for recruitment/advertisement must be reviewed and approved by the MHIRB prior to implementation or utilization.

Initial submission of research protocols must identify the method(s) of recruitment of subjects. Any advertisements to be utilized should be included with the initial protocol application.

9. Continuing Review of Research Study:

It is the investigator's responsibility to submit documentation to the MHIRB regarding the research study to have the study considered for reapproval. At the time of initial MHIRB approval of the research study, an approval time interval appropriate to the degree of risk to the subject is assigned. MHIRB Administration will send a Project Review Form to the investigator at least one month prior to expiration of research project. ***The investigator is ultimately responsible for obtaining reapproval of his/her research project; therefore, if the investigator does not receive a Project Review Form from MHIRB Administration prior to expiration of the study, it is his/her responsibility to contact MHIRB Administration to obtain this form.*** The investigator is required to submit a completed MHIRB Project Review Form to MHIRB Administration by reapproval deadline.

The MHIRB will review the reapproval application and all supporting documentation and may request additional information. The MHIRB will take action to:

- Reapprove the research study
- Reapprove the research study pending modifications to the study
- Suspend the research study pending completion of the review or the receipt of additional information
- Deny reapproval of the research study

Failure to complete and submit all required information within the specified time period may result in suspension or termination of MHIRB project approval, at which time the MHIRB is required to report the termination to the FDA and appropriate institutional officials. If the research is suspended, new subject enrollment and all study-related activities must cease, and enrolled subjects must be notified of the project status. Procedures for withdrawal of study subjects will consider the rights and welfare of the subject. Follow-up after study closure may be required, but the MHIRB must approve the follow-up once closed. Once a project is closed, it may not be reopened. A new study application must be submitted under the criteria and guidelines of MHIRB review and approval.

The MHIRB will endeavor to notify the investigator one month prior to current approval lapsing, ***but project reapproval is incumbent upon the investigator***.

The MHIRB is required to conduct continuing review of research studies, and has the authority to monitor, audit or designate a third-party monitor as the MHIRB deems necessary to ensure that studies are being conducted and documented as required. The investigator must cooperate with the MHIRB to facilitate review of research at MH.

Progress reports and final reports from the sponsor or other sources must be submitted to the MHIRB in a timely manner.

Periodic progress and other reports may be requested from the PI by the MHIRB. The PI must comply with any requests made by the MHIRB or provide justification as to the reason(s) for noncompliance.

10. Research Study Closure:

The investigator must notify the MHIRB within 3 months of closing a study. The MHIRB Project Review/Closure Form, including a listing of all subjects signing a consent, the date the consent was signed, the person obtaining the consent, a report outlining subject outcome(s), adverse events not previously reported, study withdrawals, and the reasons for the withdrawals, should be submitted to the MHIRB at the time of the study closure.

11. Documentation:

The investigator is expected to maintain all documentation required by the sponsor and regulatory agencies related to the study including case report forms and all other clinical site documentation.

The investigator is expected to maintain all correspondence from the MHIRB and copies of all correspondence sent to the MHIRB. The investigator is responsible for ensuring that all correspondence has the accurate MHIRB reference number, title and information. The documentation between investigator and MHIRB includes, but is not limited to:

- The protocol, informed consent form and all other study materials initially submitted to the MHIRB
- The MHIRB's notification to the PI of approval of the protocol and informed consent
- The PI's notification to the MHIRB of amendments and revisions to the protocol, and, where appropriate, of changes to the informed consent resulting from these amendments and revisions
- Proposed subject recruitment/advertisements sent to the MHIRB and documentation of approval of such
- The PI's notifications to the MHIRB of any serious adverse events that occurred while subjects were on study at that site
- The PI's notifications to the MHIRB of announcements by the sponsor that address adverse events at other investigative sites
- The PI's notification to the MHIRB of any change in research staff
- The PI's notification to the MHIRB in the PI's or research staff's financial, personal or professional status affecting the research study
- Notification of the MHIRB of any protocol violations or sponsor waivers
- Annual reports and any other reports of study progress sent to the MHIRB by the PI
- The PI's notifications to the MHIRB of study close-out and final report
- Copies of the PI's written responses to any MHIRB requests for changes to an informed consent, more information about an adverse event, the investigator brochure, or other requested data/information

12. Protocol/Regulatory Violations

The investigator is expected to notify the MHIRB of any reportable regulatory violations occurring at the local site. Reportable regulatory violations are those variances from the protocol that increase the risk to the research subject and/or cause or lead to harm to the research subject.

The investigator is also expected to forward to the MHIRB any reports from a study monitor concerning protocol violations at local site.

The investigator is expected to notify the MHIRB of any regulatory visits/audits or other activity that has an impact on the research or research subjects.

XX. RECORDS OF THE MHIRB

A. The MHIRB shall prepare and maintain adequate documentation of its activities including:

1. Research study file (components kept, but not limited to):
   - Protocol Summary
   - Protocol
   - Reviews by MHIRB Review Team and other experts if applicable
   - Informed consent
   - Advertisement/recruitment information
   - Investigator brochure
   - Safety information
   - Initial review and continuing review documentation
   - Adverse events
   - Changes/revisions/amendments
   - Continuing review application
   - New information provided, progress and final reports
   - Correspondence both to and from the MHIRB related to the study
   - MHIRB review and action for each of the above items

   Note: Exemption certification requests and emergency use requests records are maintained in the same manner as are other research study records.

2. Minutes of the MHIRB Meeting:
   A. Minutes are to be of sufficient detail as to show:
      - Total meeting attendance along with members absent, staff and guests attending
      - Approval of previous minutes
      - Action on each agenda item
      - Actions taken by the IRB
      - For all above action items, minutes will include the total number voting on an item, the number of members voting for, against, and abstaining from the vote, the basis for requiring changes in or disapproving research, and a summary of the discussion of issues and their resolution
      - Information items presented to the MHIRB along with discussions as occurring.
      - Reports from the Advanced Review Committed or any other ad hoc group
   B. Minutes are to be distributed to the following:
      - MHIRB members
      - MH Board of Directors, Medical Executive Committee and Medical Staff Office via the MH Administration representative responsible for operations of the MHIRB Appropriate departments as indicated
   C. Minutes are retained in written format indefinitely.

3. Accounting records related to research studies and operational budget:
   All records related to monetary transactions/budgetary issues for the MHIRB and MHIRB Administration are maintained in accordance with MH system policies and procedures and are subject to review by MH.

B. MHIRB member information:

MHIRB member information is maintained by the MHIRB Administration and includes but is not limited to:

- Name (full name with middle initial)
- Earned degree(s)
- Specialty
- Representative capacity (Status as: PS-physician-scientist; OS-other-scientist; NS-non-scientist)
- Indications of experience (such as board certifications, licenses, etc.) to show the member's chief anticipated contribution to the proceedings
- Relationship between member and the institution (i.e., employment status, member of committee, paid/unpaid consultant, stockholder, etc.)
- Curriculum vitae/résumé
- Attendance records
- Educational records (related to IRB training; date of receipt of MHIRB SOPs)
- Correspondence related to MHIRB appointment and other correspondence to or from member and MHIRB

Member information is updated as indicated. A roster of membership is available to duly authorized outside parties, but resumes, addresses and telephone numbers of members are not released without written authorization by the member.

C. MHIRB record maintenance:

The MHIRB shall maintain records for a period of at least:

- three years following the completion of a non-device, non-drug study.
- three years following the date on which the FDA approves the marketing of the drug or device for the purposes which were the subject of the study.
- five years following the date on which the results of the study were submitted to the FDA in support of the marketing of the drug or device for the purposes which were the subject of the study.
- three years following the conclusion of the multicenter study (not merely the MH investigator's portion) in situations in which the study does not result in the submission of data to the FDA for the marketing of the drug or device.

MHIRB records shall be accessible for inspection and copying by authorized representatives of the FDA at reasonable times in a reasonable manner.

MHIRB records closed for more than one year will be stored at a MH approved off site repository, but are retrievable to duly authorized individuals.

Prior membership records and rosters will be maintained for at least 3 years.

All changes to membership rosters will be sent to the OHRP and internal institutional departments in a timely manner.

D. MHIRB policies, procedures and guidelines for conducting MHIRB business:
The MHIRB maintains and adheres to written guidelines, including policies and procedures referred to as standard operation procedures (SOPs). These SOPs are in accordance with the Code of Federal Regulations and are reviewed every 2 years by the MHIRB. Changes to SOPs are made as required and implemented after review and approval by the MHIRB. SOPs are distributed to all MHIRB members with applicable portions provided in written format to PIs. Copies of all SOPs are available in the MHIRB Administration.

[21 CFR 56.108(a)(b), 21 CFR 56.115, 45 CFR 46.103(b), 45 CFR 46.108(a), 45 CFR 46.115]

XX. PROCEDURES

Only key operations are detailed in the following procedures. All operations questions should be directed to the MHIRB Administration or Chairman, MHIRB.

SOP #	MHIRB-001	
Originated	3/31/99	
Effective	3/31/99	
Review/Revised	2/2002; 3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Credential Verification of Investigators

Purpose: Individuals who conduct research must have the appropriate credentials to carry out the complete study in order to ensure subject's safety. Investigators are classified as physicians or non-physicians. Non-physician investigators are further classified as Associates of Methodist Healthcare or non-associates.

Physician Investigators

RESPONSIBILITY	ACTIVITY
Physician Investigator	1. Submit study documents to MHIRB Office 2. Submit a New Investigator Profile 3. Submit a current CV
MHIRB Administration	4. Review Medical Staff Office list of Active Physicians to verify investigator's status. If investigator is not on list, contact Medical Staff Offices for status of investigator. 5. Inform MHIRB Chair of new investigator. 6. Place CV in investigator file.
MHIRB Chairperson	7. Contact Medical Affairs Dept and appropriate department chair to verify qualifications of investigator to conduct proposed study. (if questionable) 8. Inform MHIRB Administration of qualification status.
MHIRB Administration	9. Document appropriate credential status on Project Review Checklist. **[Note: if credentials are not verified or qualifications not acceptable, notify investigator]**

Non-Physician, Associate or Non-Associate Investigator

RESPONSIBILITY	ACTIVITY
Associate or Non-Associate, Non-physician Investigator	1. Submit study documents to MHIRB Administration. 2. Submit New Investigator Profile 3. Submit current CV
MHIRB Administration	4. Determine status and refer investigator Medical Staff Office if needed. 5. Instruct investigator in process for application of privileges and to indicate to Medical Staff Services if working under auspices of physician on staff at Methodist. 6. If investigator is of student capacity, obtain signed confidentiality statement and a copy of contract, between MH and the school or affiliation agreement. **[Note: if none available, refer individual to MH Legal Affairs]**
Medical Staff Office	7. Assist investigator in completion of application for privileges. 8. Notify MHIRB Administration of privilege status of investigator, and if approved for privileges anytime stipulation on privileges.
MHIRB Administration	9. Notify Investigator of privilege status and how to proceed with study application.

SOP #	MHIRB-002	
Originated	3/31/99	
Effective	3/31/99	
Review/Revised	2/2002;3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Expedited MHIRB Review and Approval to Begin Investigation

Purpose: This SOP outlines steps Investigators must follow to gain expedited MHIRB review and approval to begin investigations.

The MHIRB's Expedited Review Committee consists of the Chair, Administrative Director or designee, and legal counsel. This committee may exercise the full authority of the IRB, except that it may not disapprove research projects or changes. A negative vote by any of the three members will result in the denial of expedited review status. In this case, the investigator must submit the materials to the full board at the next regularly convened MHIRB meeting.

RESPONSIBILITY	ACTIVITY
Investigator	1. Review expedited criteria and/or consult MHIRB Administration to determine if conditions for expedited review apply. 2. Prepare study documents for MHIRB submission. 3. Submit CV and New Investigator Profile 4. Deliver four copies of study documents and two copies of the Investigators Brochure (if applicable) to the MHIRB Administration. • Protocol (w/indication of drug or device) • Investigator Brochure (if applicable) • Informed Consent and/or Assent Form • Summary (include those authorized to obtain consent) • Conflict of Interest statement signed by PI and Co-PI • Financial Disclosure Statement • Budget (or letter indicating who handles budget) • *Note: Advertisements require full MHIRB review* ♦ IND/IDE
MHIRB Administration	5. Verify credentials of PI and research team through the Medical Staff Office 6. Enter into Study Database pertinent information regarding study 7. Assign project an IRB reference number if submitted documents are complete and credentials are verified 8. Check contents of documents for completeness at time of submission to include: • Protocol (w/indication of drug or device) • Investigator Brochure (if applicable) • Informed Consent and/or Assent Form • Summary (include those authorized to obtain consent) • Conflict of Interest statement signed by PI • Financial Disclosure Statement • Budget (or letter indicating who handles budget) • *Note: Advertisements require full MHIRB review* 9. Distribute project to the Expedited Review Committee along with a checklist. 10. If study documents are incomplete or if credentials cannot be verified, return protocol/project to PI/research team for completion. Upon receipt of completed documents, forward to Expedited Review Committee along

	with checklist. 11 Distribute Investigator Brochure (if applicable) to Pharmacy Coordinator for Investigational Drug Research. 12. File study documents copy in MHIRB study file.
Expedited Review Committee Members	13. Review MHIRB study documents and determine: • If the project meets expedited criteria . • Reasonableness of risk in relation to the benefits • Fairness and equitability of subject selection process. • Completeness of the Consent or Assent Form. • If the investigation is of a device, determine whether the investigation is a significant or non-significant risk. If determined to be a significant risk, notify sponsor of this determination and verify that the investigation is subject to an Investigational Device Exemption (21 CFR 812.66). Also if determined to be a significant risk, refer this investigation to the Full MHIRB for review and approval. 14. Communicate directly with PI or contact person for research team regarding any issues raised during review. 15. Make recommendation of the investigation (by marking the checklist) for: • Approval; • Approval pending changes; or • Disapproval for expedited review & forward for full IRB review. 16. Document review by completing recommendation at the end of the MHIRB PROJECT APPROVAL CHECKLIST 17. Return PROJECT APPROVAL CHECKLIST to the MHIRB Administration. 18. Destroy copies of study documents after MHIRB Meeting.
MHIRB Administration	19. Prepare MHIRB Response Letter to PI 20. If approved, stamp informed consent with the appropriate approval date. 21. If approval pending withhold ICF; if disapproved for expedited, notify PI 22. Send original Response Letter and stamped informed consent form to PI. 23. Update Study Database. 24. If changes required, verify changes as requested prior to sending approval letter. 25. File MHIRB Response Letter and stamped copy of Informed Consent and PROJECT APPROVAL CHECKLISTS in MHIRB study file.
MHIRB Chairperson	26. Report Expedited Review Committee action at next full MHIRB meeting.
Investigator	27. Begin investigation, if MHIRB approved, or take steps to gain MHIRB approval.

SOP #	MHIRB-003	
Originated	3/31/99	
Effective	3/31/99	
Reviewed/Revised	2/2002;3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Full MHIRB Review and Approval to Begin Investigation

Purpose: This SOP outlines steps Investigators must follow to gain full MHIRB review and approval to begin investigations.

Full IRB review of any research project involving human subjects must occur if the project:
- does not satisfy the guidelines for exemption certification, expedited review, or
- has been closed (for whatever reason) and requested to be reopened.

RESPONSIBILITY	ACTIVITY
Investigator	1. Prepare study documents. 2. Submit CV and New Investigator Profile if first time submission 3. Deliver four copies of study documents and two copies of the Investigator's Brochure (if applicable) to MHIRB Administration • Protocol (with indication of drug or device) • Investigator Brochure (if applicable) • Informed consent and/or Assent form • Summary • Conflict of Interest statement signed by PI and Co-PI • Financial Disclosure Statement (if applicable) • Budget (or letter indicating who handles budget) • Advertisements/recruitments/incentives
MHIRB Administration	1. Verify PI and research team credentials through the Medical Staff Office. 2. Check contents of study documents for completeness at time of submission. Contents to include (but not limited to): • Protocol (with indication of drug or device) • Investigator Brochure (if applicable) • Informed consent and/or Assent form • Summary • Conflict of Interest statement signed by PI • Financial Disclosure Statement • Budget (or letter indicating who handlesdget)Advertisements/recruitments/incentives 3. Assign to an MHIRB Review Team and Scientific Consultant, and assign an MHIRB reference number, if study documents are complete with credentials verified. If incomplete or if credentials not verified, then return protocol/project to PI/research team for completion. Upon receipt of completed study documents, forwarded to MHIRB Review Team 4. Inform the PI/research team of the MHIRB Review Team members and the Consultant assigned to the study/project, MHIRB reference number and projected review before full MHIRB via letter. 5. Enter into Study Database pertinent information. 6. Distribute study document copies to MHIRB Review Team and Consultant (if needed) and establish review date deadline.

	7. Distribute Investigator Brochure (if applicable) to Pharmacy Coordinator for Investigational Drug Research. 8. File copy of study documents in MHIRB study file.
MHIRB Review Team	1. Review submitted study documents and complete PROJECT APPROVAL CHECKLIST. 2. Determine: • Degree of risk to subjects. • Reasonableness of risk in relation to the benefits. • Fairness and equitability of subject selection process. • Completeness of the consent and (if applicable) assent forms. 3. If the investigation is of a device, determine whether the investigation is a significant or non-significant risk. If determined to be a significant risk, notify sponsor of this determination and verify that the investigation is subject to an Investigational Device Exemption (21CFR812.66) 4. Primary reviewer communicate with other MHIRB review team member Consultant (if needed) to discuss the submitted study. 5. Primary reviewer communicate (in writing using Review Team Form and verbally) directly with PI or contact person for research team regarding any issues raised during review. 6. Recommend study for: • Full MHIRB review; • Full MHIRB review pending changes; or • Table pending issues clarification. 7. Document recommendation by completing Recommendation Section at the end of the MHIRB PROJECT APPROVAL CHECKLIST. 8. Return Checklist to MHIRB Administration. 9. Destroy copies of study documents after MHIRB meeting.
MHIRB Administration	1. File Checklist in MHIRB study file. 2. Schedule MHIRB review and notify Principal Investigator & study coordinator (contact person) of PI's required attendance at MHIRB meeting via letter; also advise research team of number of copies of appropriate documents for final MHIRB mailout. 3. Distribute to MHIRB members the Summary form plus all information provided to subject, which includes: • Consent Form and any Assent Form • Subject recruitment/advertisement procedures • Other written information given to subject
Investigator	Attend MHIRB meeting when scheduled and present the investigation to MHIRB
MHIRB Members	1. Review Summary and all information provided to subject before scheduled MHIRB meeting. Request from MHIRB Administration any other parts of the study documents as needed to complete review. 2. Attend scheduled MHIRB meeting, listen to investigator presentation and ask questions or comment as appropriate. 3. Determine if the investigation is of a device and whether the investigation is a significant risk or a non-significant risk. If determined to be a significant risk, notify sponsor of this determination and verify that the investigation is subject to an Investigational Device Exemption (IDE). 4. Vote for one of the following: • Approve investigation with review interval no more than 12 months. • Approve investigation pending submission of recommended changes or clarification of issues. • Table investigation for further review. • Deny investigation approval.
MHIRB Administration	1. Update Study Database with pertinent information. 2. Prepare MHIRB response letter to PI 3. Stamp the informed consent with the appropriate approval date. (if approved) 4. File copy of signed MHIRB response letter and stamped informed consent form (if approved) in MHIRB study file. 5. Send original MHIRB response letter and stamped approved informed consent (if approved) to Investigator.
Investigator	Begin investigation, if MHIRB approved, or take steps to gain MHIRB approval.
	RB approved, or take steps to gain MHIRB approval.

SOP #	MHIRB-004	
Originated	3/31/99	
Effective	3/31/99	
Review/Revised	2/2002; /2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Exemption from MHIRB Review and Approval to Begin Investigation

Purpose: This SOP outlines steps Investigators must follow to gain MHIRB Exemption Certification to begin investigations.Research activities that fall into certain categories are exempt from full or expedited IRB review procedures (45 CFR 46.101(b)) except when research activities involve:

- Prisoners, fetuses, or pregnant women
- Minors
- Techniques that expose the subject to discomfort or harassment beyond levels met within daily life
- The deception of the subject

There is no deadline for submission of studies for MHIRB consideration of exemption certification.

RESPONSIBILITY	ACTIVITY
Investigator	1. Review exemption criteria and/or consult MHIRB Administration to determine if study qualifies for MHIRB Exemption Certification. 2. Prepare and submit one copy of the Exemption Certification Application to the MHIRB Administration and all study documents • Protocol • Summary with original PI and Co-PI signatures • Conflict of Interest statement signed by PI and Co-PI • Financial Disclosure Statement • Budget (either letter indicating who handles budget)
MHIRB Administration	3. Check contents for completeness at time of submission. 4. Contents to include: • Protocol • Summary with original PI and Co-Pi signatures) • Conflict of Interest statement signed by PI and Co-PI • Financial Disclosure Statement • Budget (either letter indicating who handles budget) 5. Verify credentials of PI and research team through the Medical Staff Office (see Credential Verification of Investigator procedure). 6. Assign MHIRB reference number to project and enter into Study Database. 7. Review application and make determination of approval, approval pending changes or disapproval. 8. Indicate decision on exemption certification for approval, approval pending changes, or disapproval; and sign certification. If approved, certification exemption granted for one year from date approved, with review of exemption status at end of one year. 9. Report Exemption requests and determinations at next full MHIRB meeting.
MHIRB Administration	10. Update study database with pertinent information. 11. File copy of Exemption Certification Form and study documents in MHIRB study file. 12. Send original Exemption Certification Form to principal investigator.
Investigator	13. Begin investigation, if MHIRB approved, or take steps to gain MHIRB approval.
MHIRB Administration	14. Send Exemption Certification Continuation application to PI at end of one year. 15. Review continuation application and determine if exemption certification continued or study information changes warrant review under different criteria. 16. Report review and determination of outcome at next full MHIRB meeting.

SOP #	MHRB-005	
Originated	3/31/99	
Effective	3/31/99	
Review/Revised	2/2002;3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Emergency Use of Test Article (drug or device)

Purpose: This SOP outlines steps Investigators must follow for emergency use of a test article. Test articles includes drugs, biological agents and devices. See 21CFR56.102(1) for precise definition.

Emergency use of a test article must be reported to the MHIRB within 5 working days. Any subsequent use of the test article requires a full MHIRB review.

RESPONSIBILITY	ACTIVITY
Investigator	1. Consult VP medical Affairs and MHIRB Chairman concerning intended emergency use of a test article. In absence of VPMA, PI consult with Medical Staff President or Chief of Medical Staff. In absence of MHIRB Chairman, PI consult with physician member of MHIRB. 2. Complete ONE TIME EMERGENCY USE OF TEST ARTICLE APPLICATION FORM. 3. Document Sponsor Agreement to supply test article for emergency use. 4. Submit Application and Agreement to the MHIRB Administration.
MHIRB Chairperson	5. Review ONE TIME EMERGENCY USE OF TEST ARTICLE APPLICATION FORM. Consult with Vice President of Medical Affairs (VPMA) regarding proposed emergency use of test article. In the absence of the VPMA, consult with either the Medical Staff President or the Chief of the Medical Staff. All parties must be in agreement as to intended use 6. Sign Application Form acknowledging that criteria for emergency use met. 7. Report emergency use requests at the next full MHIRB meeting.
MHIRB Administration	8. Copy ONE TIME EMERGENCY USE OF TEST ARTICLE APPLICATION FORM with MHIRB Chairperson's signature letter to PI. 9. Assign MHIRB Emergency Use study number. 10. Enter into Study Database pertinent information regarding emergency test article use. 11. File copy of Application Form, Agreement (if any) and other applicable documents in MHIRB study file. 12. Send MHIRB original Application form to principal investigator.
Investigator	13. Begin emergency test article use. 14. Provide a one month and periodic updates upon request of MHIRB.
MHIRB Administration	15. Send Emergency Use of a Test Article Follow-Up Information Form one month post-use to PI. 16. Upon receipt of response, copy to VPMA. 17. Update MHIRB Study Database.

SOP #	MHIRB-006	
Originated	3/31/99	
Effective	3/31/99	
Revised	2/2002;3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Continuing MHIRB Review of Research Studies/Protocols

Purpose: This SOP outlines steps Investigators must follow to gain MHIRB review of research studies/protocols and approval to continue investigations.

RESPONSIBILITY	ACTIVITY
MHIRB Administration	1. Run report by month indicating studies due for periodic MHIRB review 2. Notify Investigator and study coordinator, at least 1 month in advance of project approval expiration date, to prepare and submit PROJECT REVIEW FORM.
Investigator	3. Prepare PROJECT REVIEW FORM. 4. Submit PROJECT REVIEW FORM and a copy of the current informed consent form with the MHIRB approval date stamp to MHIRB Administration by reapproval deadline.
MHIRB Administration	5. Check PROJECT REVIEW FORM for completeness, and request completion of omissions from investigator. 6. Enter into Study Database pertinent information regarding investigation. 7. Complete and distribute PROTOCOLS FOR REAPPROVAL Summary Report for current month of review to ADVANCE REVIEW COMMITTEE members. 8. Schedule time for ADVANCE REVIEW COMMITTEE to review all research projects due for reapproval
Advance Review Committee	9. Meet and review PROJECT REVIEW FORMS. 10. Determine recommendation to be made to the MHIRB for each project by considering that: • Risks to subjects are minimized • Risks to subjects are reasonable in relation to anticipated benefits • Selection of subjects is equitable • Informed consent is adequate and appropriately documented • Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects • Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data • Appropriate safeguards have been included to protect vulnerable subjects 11. Communicate with PI any changes required. 12. Submit Project Reapproval Summary Report changes to MHIRB Administration.
MHIRB Administration	13. Finalize Project Reapproval Summary Report 14. Distribute final report to full MHIRB with agenda.
MHIRB	15. Review Project Reapproval Summary Report and vote to : • Reapprove investigation with review interval no more than 12 months. • Reapprove investigation pending submission of recommended changes or clarification of issues • Table investigation for further review. • Deny investigation reapproval.
MHIRB Administration	16. Update Study Database with pertinent information regarding research project. 17. Prepare MHIRB response letter.

	18. File PROJECT REVIEW FORM, MHIRB response letter and other associated material in MHIRB study file. 19. Send MHIRB response letter copy to Investigator.
Investigator	20. Continue study; take steps to reverse any disapproval to continue, or conclude study.

SOP #	MHIRB-007	
Originated	3/31/99	
Effective	3/31/99	
Revised	2/2002;3/2004	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Revision/Amendment to Studies After MHIRB Approval

Purpose: This SOP outlines the mechanism whereby revisions/amendments to a study are to be submitted and reviewed. Changes may be considered:

A. *Minor changes of an administrative nature that have no impact on subject welfare* (i.e. grammatical or typographical corrections to protocol, correction to address or phone numbers for sponsor) may be approved via the MHIRB Administration.

B. *Changes that do not eliminate apparent immediate hazards to the subject*, such as changes in the investigation plan must be submitted to and approved by MHIRB before implementation.

C. *Changes that eliminate apparent immediate hazards to the subject*, such as when a change in the investigation plan is needed to eliminate apparent immediate hazards to the subject, the change may be initiated before MHIRB approval is granted. However, MHIRB must be notified, in writing, within five working days of making a change to eliminate an apparent hazard.

RESPONSIBILITY	ACTIVITY
Investigator	1. Notify MHIRB within 5 working days of any change made to the study that that eliminated apparent immediate hazards to the subject. Notification must be in writing and REVISION/AMENDMENT FOR RESEARCH PROJECT form must be connected with an original PI signature 2. If this change does not involve removal of immediate hazards to subject, prepare and submit to the MHIRB Administration a REVISION/AMENDMENT FOR RESEARCH PROJECT form along with sponsor letter and supporting documentation prior to the change under an original PI signature. Submit 2 copies of the ICF if changed; one copy with changes highlighted and one clean copy..
MHIRB Administration	3. Enter into Study Database pertinent information. 4. Run Significant Revisions Summary Report for current month of review. 5. Schedule time for Advance Review Committee review. 6. Assign Significant Revisions to Advance Review Committee member to review. 7. Distribute Significant Revisions Summary Reports copies to Advance Review Committee members.
Advance Review Committee Members	8. Review Significant Revisions Summary Report. 9. Coordinate, with investigator, resolution of any issues. 10. Submit Significant Revisions Summary Report changes to MHIRB Administration.
MHIRB Administration	11. Finalize Significant Revisions Summary Report. 12. Distribute Significant Revisions Summary Report to MHIRB members.
MHIRB Members	13. Review Significant Revisions Summary Report and Advanced Review Committee recommendations, and take appropriate action to: • approve revisions without changing the review interval • approve revisions pending submission of recommended changes or clarification of issues • Table investigation for further review • Deny revision approval

MHIRB Administration	14. Update Study Database. 15. Prepare appropriate MHIRB Response Letter, revised consent form with new approval date (if applicable), to document MHIRB decision. 16. File signed copy of MHIRB Response Letter, REVISION/AMENDMENT FOR RESEARCH PROJECT form and supporting documentation in MHRB study file. 17. Send original MHIRB Response Letter to Investigator.
Investigator	18. Implement changes as approved by MHIRB.

SOP #	MHIRB-008	
Originated	3/31/99	
Effective	3/31/99	
Revised	2/2002	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Adverse Events at MH Reporting to MHIRB

Purpose: This SOP outlines steps Investigators follow to report adverse events. Investigators must monitor and report adverse events to the MHIRB at any time during the investigation. In addition, the Investigator must provide the MHIRB with any adverse events or other safety information received from the Sponsor at any time during the investigation. The nature of the adverse event determines how rapidly the Investigator must notify the MHIRB.

Adverse Events Reports to MHIRB

RESPONSIBILITY	ACTIVITY
Investigator	1. Submit ADVERSE EVENT REPORT along with any supporting documentation to MHIRB Administration.
MHIRB Administration	2. Upon receipt of ADVERSE EVENT REPORT, date stamp and send copy of report immediately to MHIRB Chairman
MHIRB Chairman	3. Review Adverse Event 4. Indicate decision on AE reporting form regarding disposition and medical judgment regarding event. 5. Notify MHIRB Administration of any additional information require and/or disposition of event. 6. Forward completed review form to MHIRB Administration.
MHIRB Administration	7. Enter ADVERSE EVENT REPORT into Study Database. 8. Run Adverse Event Summary Report for current month of review. 9. Schedule time for Advance Review Committee review. 10. Assign Adverse Event Report to Advance Review Committee member to review. 11. Distribute Adverse Events Summary Report copies to Advance Review Committee members.
Advance Review Committee	12. Meet and review Adverse Events Summary Reports. 13. Determine recommendations to be made to the MHIRB as needed. 14. Submit report changes to MHIRB Administration.
MHIRB Administration	15. Finalize Adverse Event Summary Report. 16. Distribute final Adverse Event Summary Report to full MHIRB with agenda.
MHIRB	17. Review Adverse Events Summary Report. 18. Take any action that may be required; otherwise, acknowledge.
MHIRB Administration	19. Prepare MHIRB Response Letter to PI. 20. File MHIRB response along with supporting documentation in MHIRB study file.

SOP #	MHIRB-009	
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Effective	3/31/99	
Revised	2/2002	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Sponsor Safety Reports (from other site) Reporting to MHIRB

Purpose: This SOP outlines steps Investigators follow to report safety reports and other safety information. Investigators must monitor and report adverse events received as sponsor safety reports to MHIRB at any time during the investigation.

RESPONSIBILITY	ACTIVITY
Investigator	1. Complete and submit SAFETY REPORT form along with the sponsor's Reports to MHIRB Administration within a reasonable time period.
MHIRB Administration	2. Upon receipt of SAFETY REPORT, date stamp receipt of documents. 3. Enter SAFETY REPORTS into Study Database. 4. Run Safety Reports Summary Report for current month of review. 5. Schedule time for Advance Review Committee review 6. Assign Safety Reports to Advance Review Committee member to review 7. Distribute Safety Reports Summary Report copies Advance Review Committee members.
Advance Review Committee	8. Meet and review Safety Reports Summary Report. 9. Determine recommendations to be made to the MHIRB as needed. 10. Submit Safety Report Summary Report changes to MHIRB Administration.
MHIRB Administration	11. Finalize Safety Reports Summary Report and distribute final Safety Reports Summary Report to full IRB with agenda.
MHIRB	12. Review Safety Reports Summary Report. 13. Take any action that may be required; otherwise, acknowledge.
MHIRB Administration	14. Prepare MHIRB Response Form and send original to PI. 15. File copy of MHIRB Response Form along with supporting documentation in MHIRB Study File.

SOP #	MHIRB-010	
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METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Closure of Research Projects by Investigators

Purpose: This SOP outlines the steps for investigators to utilize to close a research study. A research project may close due to completion of the project, a lack of project initiation at the site or a closure by the sponsor or investigator of all activities. When study objectives are met and the subject enrollment and analysis are complete, the study is deemed closed.

RESPONSIBILITY	ACTIVITY
Investigator	1. Prepare PROJECT REVIEW/CLOSURE application. 2. Submit PROJECT REVIEW/CLOSURE application and supporting documentation to MHIRB Administration.
MHIRB Administration	3. Check PROJECT REVIEW/CLOSURE application for completeness, and request omissions from investigator. 4. Enter into Study Database pertinent information regarding investigation 5. Complete and distribute Closures Summary Report for current month of review to Advance Review Committee members. 6. Schedule time for Advance Review Committee review 7. Assign research project closures to Advance Review Committee member to review.
Advance Review Committee	8. Meet and review PROJECT REVIEW/CLOSURE application. 9. Determine recommendation (if any) to be made to the IRB for each project. 10. Submit Closure Summary report changes to MHIRB Administration.
MHIRB Administration	11. Finalize Closures Summary Report 12. Distribute final Closures Summary Report to full IRB with agenda. 13. Review Closures Summary Report. 14. Take any action that may be required; otherwise, acknowledge. 15. Prepare MHIRB response letter. 16. Send MHIRB response letter copy to Investigator. 17. File PROJECT REVIEW/CLOSURE Application, MHIRB response letter and other associated material in MHIRB Study File. 18. Transfer essential document file from Active Files to Closed Files.

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METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: MHIRB Termination of Research Projects

Purpose: A research project may be closed by the MHIRB when sufficient evidence exists to question the safety of the research subjects or when there are concerns for the welfare of the research subjects, the integrity of the project, or failure of the PI to obtain reapproval of project.

RESPONSIBILITY	ACTIVITY
MHIRB	1. Upon receipt and review of pertinent information regarding project, MHIRB takes action to close or suspend project. 2. Recommend follow-up for research subjects if appropriate.
MHIRB Administration	3. Send MHIRB response letter to investigator, copied to appropriate institutional officials and the FDA. 4. Update study database. 5. File copy of letter in the MHIRB Study file. 6. Transfer MHIRB Study file from active files to closed files.
Investigator	7. Withdraw subjects from study in a manner consistent with protecting their rights and welfare. Follow-up with research subjects as permitted/required by the MHIRB.

SOP #	MHIRB 012	
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Revised	2/2002	

METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Appointment and Reappointment of IRB Members

Purpose: This SOP outlines steps for the appointment of MHIRB members. Members are appointed by the MH President upon recommendation by the MHIRB chairperson.

Note: *MHIRB members are automatically reappointed each January unless member requests or is requested to resign.*

RESPONSIBILITY	ACTIVITY
MHIRB Chairman	1. Review background, resume and record of potential MHIRB members 2. Recommend individual to MH President for appointment to MHIRB
MH President	3. Review recommendation 4. Appoint individual to MHIRB via letter
MHIRB Administration	5. Upon MHIRB candidate's acceptance of appointment amend MHIRB membership roster to include new member 6. Send update to appropriate officials (OHRP, etc) 7. Establish new MHIRB member record including CV, address and letter of appointment, date of appointment and acceptance letter 8. Maintain attendance records of MHIRB member at meetings and training sessions 9. Annually, each December, review MHIRB member attendance records and report findings of nonattendance to MHIRB Chairman.

SOP #	MHIRB 013	
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METHODIST HEALTHCARE INSTITUTIONAL REVIEW BOARD (MHIRB)
STANDARD OPERATING PROCEDURE (SOP)

Originator: MHIRB

Procedure: Accounting of MHIRB Study Fees

Purpose: This SOP outlines steps for the receipt, deposit and recording of IRB fees received from studies submitted to the MHIRB.

Note: All accounting procedures are in accordance with established MH system policies and procedures.

RESPONSIBILITY	ACTIVITY
MHIRB Administration	1. Upon receipt of study for review and determination as to type of review (exemption, expedited, full), produce invoice and mail to PI or designated contact person for study. 2. Enter fee information in database.
Investigator	3. Submit appropriate fee to MHIRB.
MHIRB Administration	4. Upon receipt of payment of fee, copy check and deposit fee into MHIRB Administration cost center revenue account (using account number designated by Finance.) 5. Enter receipt of payment into database, indicating date paid. 6. Stamp invoice paid and attach copy of check and account deposit receipt. 7. Quarterly review outstanding invoices and notify appropriate contact person for the study that is outstanding. 8. Monthly reconcile deposit receipts with monthly financial statement for cost center.

XXII. APPENDICES

1. Adverse Event Report Form

   Adverse Event MHIRB Medical Review and Chairman Response
2. Advertising Guidelines
3. Assent Form Guidelines
4. Closure Form
5. Credential Verification Form
6. Disclosure and Description of Financial Interests Related to Sponsored Research Projects Form
7. Emergency Use Request Application
8. Emergency Use Follow-up Information
9. Exemption Certification Application
10. Exemption Certification Continuation Form
11. Fee Structure and Fee Waiver Request Form
12. FederalWide Assurance Document (FWA)
13. Glossary and Abbreviation List
14. Informed Consent Form Template
15. Informed Consent Guidelines
16. Medical Record Research Request Form
17. Meeting Schedule of MHIRB
18. Membership Roster of MHIRB
19. New Investigator Profile Form
20. Primary Review Forms for:
    - Full review
    - Expedited review
    - Cooperative Agreement review studies
20. Project Approval Checklist
21. Reapproval Project Review Form

22. Regulatory Documents and Resources

- Belmont Report
- Subject Bill of Rights
- Declaration of Helsinki
- Nuremberg Code
- 45CFR46 (Common Rule)
- Web Sites

23. Revision to Research Project Form

24. Review Requirements (forms to submit for review, etc)

- Exemption Certification requirements
- Expedited Review requirements
- Full Review requirements

25. Safety Report Form

26. Study Summary Form

Note: Methodist Healthcare system policies pertaining to research and the MHRIB can be found on the Methodist Healthcare intranet (MOLLI) or obtained in hard copy from the MHIRB Administration.