Tallahassee Memorial Healthcare, Inc

Institutional Review Board Guidelines

(signature on file)

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Chair, Institutional Review Board
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SECTION 1

Goals and Scope of the IRB

1.1 Goals

The Institutional Review Board (hereafter referred to as the IRB) at Tallahassee Memorial HealthCare, Inc. (hereafter referred to as TMH) was established in accordance with Federal regulations pertaining to the Protection of Human Subjects under the National Research Act of 1974, Title 21 CFR Parts 50, 54 and 56, and Title 45 CFR Part 46 (as amended). All research involving human subjects at TMH must be submitted in writing and approved by the IRB.

The IRB will be guided by the ethical principles in The Belmont Report. It will comply with the Terms of Assurance for the Protection of Human Subjects as required in TMH's Federalwide Assurance as approved by the Department of Health and Human Services (DHHS) Office of Human Research Protection (OHRP).

The primary goal of the IRB is to assure that the rights and welfare of the human subjects involved in research at TMH are adequately protected and that human subjects are not exposed to inappropriate risks. To achieve this goal, the IRB will:

1. review all planned research involving human subjects prior to initiation of the research
2. approve research that meets established criteria for protection of human subjects as well as their private health information, to the extent possible
3. monitor approved research to ensure that human subjects have given informed consent to participate in the research and that human subjects remain protected during the course of the study.

1.2. Scope - Human Subjects Research at TMH

Any systematic investigation that is designed to develop or contribute to generalizable knowledge, and which involves living humans about whom an investigator obtains information through intervention or interaction or obtains identifiable private information, qualifies as human subjects research. Also, any activity whose data will be submitted to the FDA or held for their inspection, qualifies as human subjects research.

Interventions in human subjects include physical procedures by which data are gathered, and manipulations of the subject or the subject's environment for research purposes.

Interactions with human subjects include communications or interpersonal contacts conducted for research purposes.

Private information includes information collected under circumstances in which the subject would not reasonably expect to be observed or recorded, and information the

subject can reasonably expect will not be made public in a manner exposing the identity of the subject.

IRB approval is required whenever human subjects are involved in the following:

1. Research is to take place on the premises of any TMH facility;
2. Research is to take place elsewhere, and involves an employee / affiliate of TMH
3. Research is to take place elsewhere, utilizing data collected on current patients, research subjects or staff / affiliate of TMH or related facilities, including those data stored in any form, off the premises of TMH or related facilities.

At its discretion, the IRB may accept for review and approval research projects that are to take place elsewhere off the premises of TMH or related facilities if there is involvement of members of the staff / affiliate of TMH.

1.3 Human Rights Research Exempt from IRB Review

Research investigators who intend to use human subjects in research activities do not have the authority to make an independent determination that the research is exempt from applicable regulations. All studies need to be submitted to the IRB Office for review and determination.

SECTION 2

Authority, Duties and Responsibilities of the IRB

2.1 Institutional Authority

The responsibility for compliance with federal, state and Tallahassee Memorial Health Care, Inc. (TMH) regulations concerning activities involving human subjects and for assuring the protection of human subjects rests with the TMH Board of Directors. The Board of Directors has delegated this authority to the President/Chief Executive Officer (CEO) of TMH, who is legally authorized to act for the institution and to assume, on behalf of the institution ("Signatory Official"), the obligations under TMH's Federal Wide Assurance (FWA) with the Department of Health and Human Services (DHHS).

TMH has designated the Institutional Review Board (IRB) to provide oversight for all research conducted under its FWA with DHHS. The IRB acts under the authority of the President/CEO.

TMH bears full responsibility for the performance of all research involving human subjects and for the protection of the rights and welfare of human subjects under its Assurance with DHHS, including complying with federal, state, or local laws as they may relate to such research and protections.

2.2 Functions

The functions of the IRB include the following:

1. Review all research protocols involving human subjects before the involvement of human subjects;
2. Approve, modify or disapprove new research projects and continuation of previously approved projects;
3. Review and approve the methods that investigators propose to use to recruit participants;
4. Determine which studies pose significant or non-significant risk
5. Review revisions in research protocols and informed consent documents as a condition for initial or continuation approval;
6. Monitor the activities in approved projects, in any way deemed necessary, including regularly scheduled progress reports at least every twelve months, to verify compliance with approved research protocols and informed consent procedures; determine which studies require review more often than annually;
7. Review reports of any planned changes in approved projects so that no material changes occur without prior approval by the IRB;
8. Review reports of any severe adverse events occurring in approved projects.
9. Suspend or terminate an approved project that is not being conducted in accordance with IRB's requirements or that has been associated with unexpected serious harm to subjects;
10. Review and monitor the use of test articles (investigational drugs and devices) for the purpose of treatment of serious or life-threatening illnesses
11. Ensure prompt reporting to the IRB, appropriate institutional and the FDA of: unanticipated problems involving risk to subjects or others; other serious or continuing noncompliance with 21 CFR parts 50 and 56 or the requirements of the IRB; suspension or termination of IRB approval.
12. Report, in writing, findings and actions of the IRB to the primary investigator; the investigator is responsible for communicating IRB decisions to the sponsor, other institutions and agencies.

The IRB will employ a review process which conforms to the Federal Policy for Protection of Human Subjects, the regulatory codes 45 CFR 46 of the HHS and 21 CFR 50, 56, 312 & 412 of the FDA, and the current Federalwide Assurance (FWA). The review process will be the same for all research involving human subjects conducted at TMH.

2.3 Responsibilities

The IRB membership is responsible for complying with and ensuring compliance with federal regulations for the protection of human subjects and applying ethical principles in the review of research in order to protect human subjects

SECTION 3

TMH Research Council and IRB Administration

3.1 The Research Council

The purpose of the Research Council is to provide administrative oversight of clinical and socio-behavioral research studies at TMH. The Council represents TMH and is responsible for determining what impact a study will have on the organization.

The Council reviews all new, academic and socio-behavioral studies whenever there is request for:

1. Access to the medical record without an informed consent (requires use of an honest broker)
2. Use of TMH resources
3. Waiver of IRB fee
4. Waiver of honest broker fee

The Council considers the operational impact of the study to include: clinical, administrative, financial, operational, risk, legal and regulatory issues and implications related to the research study. This includes but is not limited to the following, as applicable:

1. Budget (TMH costs related to the study, billing, revenue)
2. Product approval team (PAT) approval
3. Impact on non-research staff and / or departments (study feasibility)
4. HIPAA Privacy and Security
5. IT resource requirements
6. Contracts
7. Regulatory Requirements

The Council solicits input from TMH service line administrators, directors and department managers who may be affected by the study to determine impact and resource availability.

The Council ensures that TMH has effective processes and documentation to support and manage the clinical research and socio – behavioral studies and activities.

Members of the Council include: VP/CIPO, VP/CFO, VP/CNO, VP/CIO, President / CEO TMH Foundation and the Chief Compliance Officer. Ex Officio members may be: Risk Manager, General Counsel, and Regulatory Readiness Coordinator.

3.2 IRB Administration

The IRB Administrative Liaison has oversight for the IRB and Honest Broker programs and the Director of Patient Safety has responsibility for the IRB Office staff.

The IRB office staff includes a Coordinator and an Analyst / Advisor.

Specifically, the IRB office staff is responsible for:

1. compliance with applicable federal and state regulations and laws, TMH policies, and ethical obligations to protect human subjects;
2. assisting with the preparation, monitoring, and documentation of IRB Meetings;
3. maintaining files on human subjects' research;
4. maintaining the database for tracking studies;
5. receiving, reviewing, preparing, and distributing submissions for review;
6. preparing, distributing, and maintaining the IRB meeting and informational minutes;
7. screening all research submissions (including new applications, continuing review submissions, revisions, tabled items, miscellaneous items, etc) for completeness and compliance with acceptability standards prior to initiating the IRB review process;
8. acting as a resource for investigators and research team members on general regulatory information, guidance with IRB forms, and assistance with the preparation of submissions for IRB review;
9. generating and sending reports of all IRB decisions to Investigators, which include, but are not limited to, notices of approval, study closure, and termination for applicable projects;
10. sending reports of applicable IRB decisions to appropriate individuals / organizations / agencies:
11. generating and sending reminder notices to investigators of upcoming continuing reviews;
12. corresponding with principal investigators to inform them of IRB decisions, required revisions, and requests for additional information/documentation to assist with the IRB decisional process.

3.3 Office of Research / IRB Contact Information

The Office of Research / IRB is located at 1310 Magnolia Drive, Tallahassee Fl, 32308. Hours of operation are 8:30 AM to 5:00 PM, Monday through Friday. The phone number is 850 431 5676; the e-mail is IRBOffice@tmh.org; and the website is https://www.tmh.org/for-healthcare-professionals/irb.

Section 4

IRB FEES

4.1 IRB Fees

Fees may be charged to applicants as established by the IRB. All fees are non-refundable whether or not the study is approved by the IRB. IRB fees should be considered in the budgeting process when developing the study protocol.

1. The initial application fee is $1,500 payable at the time the study is submitted for review.
2. The progress review application fee is $500 payable at the time the study is submitted for review.
3. There is a $50 fee for modifications to the study.
4. There is a $25 / hour fee, if an the honest broker is used

Fees are paid by check, credit card or journal transfer to the IRB through the Office of Research/IRB. The fees paid by check are made payable to TMH.

4.2 IRB Fee Waivers

IRB fees may be waived on a case by case basis for single-patient use, emergency use, exempt research and unfunded student /colleague protocols by the TMH Research Council. Principal investigators requesting a fee waiver must explain the circumstance surrounding the need for the waiver on the Fee Form IRB Form 6. This form also serves as the billing invoice for sponsors.

Section 5

IRB Membership

5.1 IRB Membership

IRB will conduct its business with the participation of voting members and if needed, ad hoc reviewers.

5.2 Composition of IRB

Federal regulations 45 CFR 46.107 and 21 CFR 56.107 outline the requirements for the composition of institutional review boards and require the Board to:

1. have at least five members with varying backgrounds to promote complete and adequate review of the research activities commonly conducted by the institution;
2. make every nondiscriminatory effort to ensure that the membership is not composed of entirely men or entirely women;
3. include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas;
4. include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution; and

5. not allow any member to participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

The IRB, at its discretion, may invite scientists or non-scientists from within or outside of TMH who are not members of the IRB and who have special expertise to function as ad hoc reviewers of a project application to assist the IRB in its review process. These ad hoc reviewers will have access to all documents submitted to the IRB relevant to the specific project under review, may participate at the deliberations and make recommendations on the project, but may not vote.

When the agenda includes protocols that involve vulnerable populations, the Office of Research/IRB staff is responsible for ensuring that at least one member attending the meeting has knowledge and experience in working with the study population.

5.2.1 Alternates Alternate board members replace voting members who are, on occasion, unable to attend convened meetings of the IRB. Alternates members may attend all convened meetings but are non-voting members unless in the place of the primary voting member, in which case they become voting members. When alternates substitute for a voting member, the alternate will review the same materials that were assigned to the full member. The IRB minutes document when an alternate member replaces a voting member.

5.3 Appointment of Chairperson / Vice Chairperson

The IRB will have a chairperson who has the qualifications of a scientist member of the IRB, is concerned about human rights and ethical issues, is well-informed in regulations relevant to the use of human subjects in research, and has served on the IRB for at least two years.

The chairperson will be appointed by the President/Chief Executive Officer (CEO) for renewable two-year terms. This is indicated in the appointment letter.

The process for the renewal of the term of appointment of the chairperson will be initiated by the majority of the voting IRB members. The request for renewal will be submitted by the IRB membership to the President/CEO for approval. If the current chairperson does not wish to extend his/her appointment, or the IRB or President/CEO does not approve the reappointment, the procedures for the selection of a new chairperson will be activated. The IRB may provide, or the President/CEO may request, the nomination of more than one eligible member of the IRB. The President/CEO will approve one of the nominees for appointment.

The IRB Chair is evaluated by the President/CEO, with input from the IRB Administrative Liaison on an annual basis. The major criteria for the evaluation are knowledge of IRB regulations, attendance at Board meetings and leadership of the IRB, support of the IRB staff and availability to deal with IRB related issues from investigators.

The Chair will appoint a Vice-Chair. This role is filled by an experienced member of the IRB to assume the responsibilities of the chairperson during any period of the

chairperson's absence. Whenever the chairperson or vice-chairperson is not available, the chairperson may designate a senior member of the IRB to assume the responsibilities of the chairperson during the period of his/her absence.

5.4 Terms and Conditions of Service / Chairperson

The Chair has full voting rights, with the exception that s/he may not participate in a committee decision on a matter in which s/he has a conflict of interest, as defined in "Conflict of Interests."

Upon appointment to the IRB, a current copy of Chair's Curriculum Vitae (CV) must be provided to the IRB and maintained on file. Updated copies of members' CVs are requested as re-appointments are made to the IRB.

The Chair of the IRB is expected to read all new protocols, continuing review protocols, amendments/revisions/adverse event reports, ethical issues pertinent to human subject protections and other administrative meeting materials before a meeting and to facilitate the meeting discussions.

The Chair of the IRB is expected to act on behalf of the IRB in reviewing and approving the expedited and exempt study materials submitted between IRB meetings, provide consultation to Board and Office of Research/IRB staff regarding research topics.

The Chair of the IRB is expected to attend all scheduled meetings of the IRB. When the Chair is unable to attend a scheduled meeting of the IRB, arrangement should be made in advance with the Vice-Chair or another senior Board member to facilitate the meeting. This information should be provided to the Office of Research/IRB.

A chair who is absent without notifying the Office of Research/IRB two meetings in a row or who is unable to attend at least 20% of the meetings in a rolling year may have her/his membership on the Board terminated.

When the Chair is not able to attend a scheduled meeting of the IRB sufficient advance notice should be provide to the Office of Research/IRB of the intended absence(s), preferably at least ten working days. A suitable substitute should be appointed to chair the meeting. It is expected that such instances will be infrequent.

5.5 Nomination for Membership

The IRB solicits nominations for membership. A nominating sub-committee will be assembled, as needed.

It is incumbent upon the individual nominating the candidate for review to discuss the submission and determine the candidate's interest in the position. The candidate should be informed of the obligations of being a Board member prior to the nomination. The CV/resume of the recommended candidate(s) is submitted to the Board for approval. The nominated member is submitted to the President/Chief Executive Officer (CEO) of TMH for appointment to the IRB.

5.6 Terms and Conditions of Service / Members

Members are appointed for three-year terms. This is indicated in the appointment letter. The term of membership will be renewable for additional three-year periods without limit, as long as a member continues to possess the required qualifications. In case a member is chosen to become the chairperson, the duration of his/her membership will be extended automatically, to allow completion of the term of appointment as a chairperson.

In the case of reappointment, the IRB chairperson will review with a member in the last year of a three-year term the suitability of continuation into the next three-year term. If the consensus is continuation, the chairperson will recommend the reappointment to the President/CEO.

Each regular IRB member has full voting rights, with the exception that a member may not participate in a committee decision on a matter in which he/she has a conflict of interest, as defined in "Conflict of Interests."

Upon appointment to the IRB, a current copy of each member's Curriculum Vitae (CV) must be provided to the IRB and maintained on file. Updated copies of members' CVs are requested as re-appointments are made to the IRB.

All IRB members are expected to read all new protocols, continuing review protocols, amendments/revisions/adverse event reports, ethical issues pertinent to human subject protections and other administrative meeting materials before a meeting and to participate in meeting discussions.

Members of the IRB are expected to attend all scheduled meetings of the IRB. Members who are absent without notifying the Office of Research/ IRB three meetings in a row or who are unable to attend at least 50% of the meetings in a rolling year may have their membership on the Board terminated.

Members of the IRB who are not able to attend a scheduled meeting of the IRB should provide sufficient advance notice of the intended absence(s), preferably at least 15 working days, to the Office of Research/IRB. It is expected that such instances will be infrequent.

The IRB reserves the right to reschedule protocols for review based on the experience and expertise of the members attending the IRB meeting and/or to seek expert consultation if deemed necessary.

5.7 Compensation

Voting members of the Board are provided a parking voucher for each meeting attended and may receive an honorarium of $160. The honorarium is to recognize the work done in preparation for the meeting. It is not for merely attending the meeting.

5.8 Non-voting Members

The IRB Chair and Regulatory Readiness Coordinator appoint non-voting members as needed to provide a particular expertise or consultation that may add to the benefit of the Board. Representatives from the Finance Department, the Regulatory Readiness Coordinator and the Analyst / Advisor serve as non-voting members.

Non-voting members do not count toward the meeting quorum.

Non-voting IRB members are not compensated for their service on the IRB (i.e., for attending meetings and for reviewing the protocol or other information).

5.9 Removal of Member

When a Board member consistently fails to attend IRB meetings or fails to meet expectations, the IRB Chair and Regulatory Readiness Coordinator or Administrative Liaison meet with the Board member to determine the cause. If the IRB member indicates an inability to continue to function effectively as an IRB member, the member will be thanked for her/his service on the Board and relieved of her/his post. The Board will be notified at the next scheduled IRB meeting of the vacancy. Nominations to fill the position will be sought and a subcommittee convened if necessary.

Members who do not adequately fulfill their responsibilities, as judged by the IRB Chair may be asked to step down from IRB membership by the Chair and/or IRB Administrative Liaison or Regulatory Readiness Coordinator.

Members of the IRB may be removed before the end of their term if their participation in IRB activities is deemed to be inadequate, inappropriate, or damaging to the reputation of TMH and its research activities.

5.10 IRB Performance Review

The IRB is routinely evaluated for performance, composition, and attendance by the IRB Chair and the Regulatory Readiness Coordinator or IRB Administrative Liaison. The Regulatory Readiness Coordinator and IRB Administrative Liaison meet with the IRB Chair as needed for "state of the IRB" discussions and feedback is freely exchanged about what Board activities need to be addressed, updated, clarified, and the IRB Chair identifies administrative office issues that the Regulatory Readiness Coordinator and IRB Administrative Liaison need to address. In addition, Board members may also be asked to complete a self evaluation.

5.11 IRB Member Conflict of Interest

No member of the IRB may participate in the initial, continuing review (may provide information or clarification as necessary but may not vote), or amendment of any protocol in which the member has a conflict of interest. Serving as an investigator or co-investigator on a study is always a conflict of interest. Conflicts of interest may be either financial or non-financial.

At a convened meeting of the IRB, any member who has a conflict of interest must leave the room and not participate in the vote on the relevant protocol. The absent IRB member does not count toward the meeting quorum. Absence from the meeting due to conflict of interest is documented in the minutes of the meeting. The same policies apply to an IRB Chair or Vice-Chair performing expedited reviews.

5.12 Confidentiality of Protocol Submissions

IRB members will treat all information submitted for review as confidential material. These materials may not be distributed to non-IRB members or staff not associated with the IRB

5.13 Orientation and Education

New members of the IRB will receive a letter of appointment and meet with the IRB Chair and Regulatory Readiness Coordinator. The orientation session will review the functions of IRB members, discuss the confidentiality rules of the IRB, and review the member conflict of interest policy. Each new member is provided with an extensive outline of important topics and given various references for information on those topics. Opportunities for additional education are also provided.

IRB members must show proof of training in human subjects protection. Relevant articles are routinely distributed to IRB members to further their knowledge and educational opportunities are provided at the IRB meetings enhance members' knowledge of regulations and information relating to protection of human subjects.

5.14 Liability Coverage for the IRB Membership

Tallahassee Memorial HealthCare, Inc. will indemnify IRB members against liability incurred while performing actions that fall within the scope of their duties as IRB members.

Section 6

IRB Meetings

6.1 IRB Meetings

IRB members will convene approximately once every month to oversee research involving human subjects at TMH. The IRB will have an agenda for each of its meetings that includes:

1. Call to order
2. Quorum and Alternant
3. Conflict of Interest
4. Board Business and Continuing Education
5. Approval of Minutes

6. Full Board Reviews of Risk / Minimal Risk Applications
    - Initial applications
    - Renewal Applications
    - Modifications / Amendments
    - Internal Unexpected and Related SAEs / AE, Major Deviations / Violations/ Unanticipated problems/ Protocol Exceptions
    - External SAE/AE
    - Annual Reports, SSMB Reports, Final Reports, Publications
7. Expedited Approvals
    - Initial Applications
    - Renewal Applications
    - Modification Requests- Expedited
    - Expedited Internal Minor Unanticipated Problems / Deviations / Violations/ Protocol Exceptions
8. Exempt Approvals
9. Closed, Terminated or Withdrawn Studies
10. Old Business
11. Next Meeting
12. Adjournment

6.2 IRB Review Materials

The IRB review materials are electronic and include materials to be covered at the full Board meeting. The review documents are available at https://tmh.imedris.net/ at least 10 calendar days in advance of scheduled meetings. The review materials will include those items on the IRB agenda.

6.3 IRB Quorum

With the exception of applications eligible for expedited review, a quorum of the IRB membership must be present in order to conduct business. A quorum requires the presence of a simple majority (50% +1) of the voting members of the IRB, including at least one of its non-scientific members and one scientific member. The Chairperson, or in the absence of the chairperson, an experienced member of the IRB (Vice-Chair) will chair the meetings. IRB members will notify the Regulatory Readiness Coordinator for the IRB prior to the meeting date if unable to attend. If a quorum will not be present at a meeting, the Regulatory Readiness Coordinator for the IRB will notify the IRB Chairperson and reschedule the meeting. Should the quorum fail during the meeting (i.e., loss of majority through recusal of members with conflicting interest or early departures, or absence of nonscientific member) the IRB may not take further action or votes until the quorum is restored. This action shall be recorded in the minutes.

Proxy votes, either written or via telephone, are not allowed

Whenever a research project application is being reviewed in which a member of the IRB may have a potential conflict of interest, that member will leave the site of the IRB meeting during action on the application.

6.4 Review Process

All IRB members receive complete study documentation for review. In addition, primary and secondary reviewers are assigned to lead the discussion for the individual studies. Interval and annual reports are assigned a single reviewer.

Research investigators of new, full board studies are expected to attend the IRB meeting to provide information, clarify issues and answer questions related to the protocol. The investigator will be asked to leave the meeting during the discussion, deliberation and voting phase of the review process.

6.5 Risk/Benefit Determination

One of the major responsibilities of the IRB is to assess the risks and benefits of proposed research. The risks and benefits are considered in the realm of probability since the outcome of the study is to be determined. The IRB determines risks associated with studies from the perspective of the conditions that make a situation dangerous *per se*. The risk should be justified by the anticipated benefits to the subjects or society.

Identification and Assessment of Risks: In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with **therapies** subjects would undergo even if not participating in research, should be considered. It is possible for the risks of the research to be minimal even when the therapeutic procedure presents more than minimal risk. Sometimes a fine line may be drawn when attempting to distinguish therapeutic from research activities.

The potential risks faced by research subjects may be posed by design features employed to assure valid results as well as by the particular interventions or maneuvers that may be performed in the course of the research. Subjects participating in a study whose research design involves **random assignment** to treatment groups face the chance that they may not receive the treatment that turns out to be more efficacious. Subjects participating in a **double-blind** study take the risk that the information necessary for individual treatment might not be available to people who need it when needed. In behavioral, social, and some biomedical research, the methods for gathering information may pose the added risk of invasion of **privacy** and possible violations of **confidentiality**. Many risks of research are the risks inherent in the methodologies of gathering and analyzing data, although the more obvious risks may be those posed by particular interventions and procedures performed during the course of research.

Identifying Significant Risk vs. Non-significant Medical Devices

The FDA charges the sponsors with the responsibility for making the initial risk determination and presenting it to the IRB. Unless the FDA has already made a risk determination for the study, the IRB must review the sponsor's Significant Risk or Non-significant determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the Significant Risk or Non-significant determination for the study, then the FDA's

determination is final. FDA is available to help the IRB when making its risk determination.

The IRB may approve non-significant risk device studies. If the IRB determines that a study submitted as a non-significant risk device study is a significant risk study, the study shall be tabled pending proof of FDA approval of the sponsor's IDE applicant for a significant risk study. This action will be documented in the minutes and in writing to the investigator.

6.6 IRB Meeting Minutes

The IRB staff will prepare and maintain minutes of each IRB meeting. The minutes will be in sufficient detail, and will include the following:

1. Attendance, including guests;
2. Vote on minutes of the prior meeting;
3. Decisions reached on each research project application reviewed and each research project receiving continuation review;
    - Detail should describe the reason for the risk (significant or non-significant) / benefit determination.
    - Members vote on the decisions, documenting the total number of votes for; votes against; and members abstaining and noting IRB members who absent themselves from the meeting room when IRB reviews research in which they may have a conflict of interest.
    - Reasons for requiring changes in a project, or tabling, disapproving, suspending or terminating a project.
    - If vulnerable groups of subjects are included in the research, the justification for their inclusion, and adequacy of special precautions taken to minimize risks.
    - Summary of the discussion of disputed or controversial issues and their resolution.
    - *[OHRP recommends minutes clearly reflect determinations regarding risk and approval period **if** (review interval **will be** less than annually)].*
4. Proposed changes in protocol, and associated votes;
5. Amendments and revisions to the study and informed consent documents;
6. Serious Adverse Events (SAE) Summary document, SAE reports which occurred at TMH and related facilities, and actions taken;
7. Close out reports and withdrawn protocols;
8. Emergency / compassionate use reports;
9. Expedited reviews;
10. Educational material distributed, and pertinent discussion;
11. Changes in membership;
12. Reason for calling special meetings;
13. Miscellaneous items;
14. Date of next scheduled meeting;
15. Announcements and other business items.

Section 7

IRB Categories of Review

7.1 Categories of Review Overview

The IRB reviews, requires modification, and approves or disapproves all human subjects research conducted at TMH. The IRB will comply with federal regulations at 45 CFR 46.111 (DHHS) and 21 CFR 56.111 (FDA), institutional policies, state regulations, and the terms of the Federal-Wide Assurance (FWA) between TMH and DHHS in order to determine whether protections for human research subjects are adequate.

7.2 Exempt Review

Exempt review is reviewed by IRB Chair/designee but NOT subject to continuing review. Exempt status will be determined by the staff of the Office of Research/IRB in conjunction with the IRB chair/designee, according to criteria outlined in 45 CFR 46.101 (b). The term "exempt" means the research will be reviewed for approval by the IRB chair or designee and will not be subject to continuing review under federal regulations. Research involving prisoners, fetuses, pregnant women, or human in vitro fertilization is not eligible for exempt review.

Category 1 - Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Category 2 - Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. For research that involves children as subjects, no exemptions are allowed under (b) when subjects are involved in observations in which the investigator participates in the activities being observed.

Category 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 (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter

Category 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.

Category 5 - Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and are designed to study or evaluate:

- Public benefit or service programs;
- Procedures for obtaining benefits or services under those programs;
- Possible changes in or alternatives to those programs or procedures; or
- Possible changes in methods or levels of payment for benefits under those programs.

Category 6 - Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Criteria used to determine if a research project qualifies as exempt from continuing review may be found at 45 CFR 46.101 (b). Final determination of exempt status will be made by the staff of the Office of Research/IRB in conjunction with the IRB Chair or designee.

When an investigator believes his study meets the criteria for research exempt from continuing IRB review, he must submit it as such to the Office of Research/IRB (see Requirements for New Study Submission).

If the application qualifies for exempt review, the Office of Research/IRB will notify the investigator in writing of its determination. The letter will cite the specific category under which the research qualifies as exempt, and will be signed by the Administrative Liaison/IRB or IRB Chair or designee.

If a protocol does not qualify as exempt, the investigator will be advised in writing to submit the protocol to the IRB for either expedited or full board review.

Research to be considered for exempt status is not subject to deadline dates. Protocols will be reviewed as they are submitted to the IRB. If it is determined that a protocol does not qualify as exempt and requires expedited or full-board review, the protocol may be resubmitted under the appropriate category. Deadline dates apply to the submission for full board review only.

Protocols classified as exempt are not subject to continuing review. However, it is the investigator's responsibility to notify the IRB of any changes or modifications that are made in the research study design, procedures, etc. Such changes may necessitate a new IRB submission. Protocols approved as exempt will be assigned an IRB Protocol Number that must be referenced on all correspondence with the Office of

Research/IRB.

7.3 Expedited Review

Expedited review is research reviewed by IRB Chair/designee and is subject to continuing review. Expedited review shall be used for research activities that meet the criteria outlined in 45 CFR 46.110 and 21 CFR 56.110. Expedited review shall not be used to approve any research that includes genetic testing, or any research involving children or other vulnerable populations. The IRB Chair or designee shall have the same authority as the IRB except they may not disapprove the research. A research activity may be disapproved only after full-board review. The IRB will use the expedited review procedure to review research activities that:

- Present no more than minimal risk to subjects; and
- Involve only procedures listed in one or more of the categories allowed by DHHS, available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.110.

These categories have been provided by DHHS as areas of research that **may** qualify for expedited review. Although a specific research procedure may fall within these categories and be eligible for expedited review, the research may be determined to be greater than minimal risk after consideration by the expedited review procedure and may be referred for full IRB review. The standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review.

Research submitted for expedited review is not subject to meeting cycle deadline dates. Protocols are reviewed as they are submitted. The term “expedited” refers to the type of review mechanism that is employed and does not necessarily mean “quicker”. If it is determined that a protocol does not meet the criteria for expedited review and requires full-board review, deadline dates would apply to the resubmission.

If a research protocol meets the criteria and is eligible for expedited review, the IRB Chair or designee(s) with the appropriate expertise to review the protocol will carry out the review. The full protocol, including the consent form and all pertinent source material, will be considered. The IRB Chair or designee(s) will have the same authority as the IRB in reviewing the protocol, with the exception that the protocol cannot be disapproved via this procedure. A decision for disapproval must be rendered by the full Board using the procedure for full IRB review. When a protocol is approved through expedited review, the specific permissible category under which it qualifies will be cited in the approval letter and the IRB meeting minutes.

7.4 Full Board Review

Full board review is research reviewed by a convened meeting of the IRB and is subject to continuing review. Full board review at a convened IRB meeting with a quorum present will be required for all new research protocols that do not qualify for exempt or expedited review. The IRB Chair or designee will determine the appropriate category of review based on the type of research to be conducted. Continuing review, protocol and consent form modifications, adverse event reports, and other related

research activities will be reviewed by expedited or full-board review procedures as appropriate, using criteria at 45 CFR 46.110 and 21 CFR 56.110.

The full protocol, including the consent form, all pertinent source material, and all required IRB forms are reviewed by the full IRB for their consideration. In addition to scientific expertise, consideration will be given to special issues and populations. Consultant reviewers with the necessary expertise to augment the Board's review will be invited to review protocols and accompanying materials.

The principal investigator will present the project to the IRB membership and answer questions at a scheduled Board meeting. The investigator may not be present during the vote on the protocol to avoid undue influence on IRB members.

The Board is responsible for detailing any issues and concerns to allow the PI provide the information necessary to allay any concerns and assist in the determination of the level of risk the research presents, i.e., significant risk or non-significant risk. The Board's decision will be based on the vote of the majority of the voting members present.

Section 8

Investigator Responsibilities

8.1 Who is an Investigator at TMH?

Investigators can include physicians, scientists, nurses, administrative staff, teachers, and students, among others. Some research studies are conducted by more than one investigator, and usually one investigator is designated the "principal investigator" with overall responsibilities for the study.

8.2 Investigator Responsibilities

In every human subjects research study, investigators have certain responsibilities regarding the ethical treatment of human subjects

The Health and Human Services (HHS) regulations, at 45 CFR 46, use of the term "investigator" to refer to an individual performing various tasks related to the conduct of human subjects research activities, such as obtaining informed consent from subjects, interacting with subjects, and communicating with the IRB. For the purposes of the HHS regulations, Office of Human Research Protections (OHRP) interprets an "investigator" to be any individual who is involved in conducting human subjects research studies. Such involvement would include:

- obtaining information about living individuals by intervening or interacting with them for research purposes;
- obtaining identifiable private information about living individuals for research purposes;

- obtaining the voluntary informed consent of individuals to be subjects in research; and
- studying, interpreting, or analyzing identifiable private information or data for research purposes.

When a study is conducted in collaboration with another organization or sponsor, the originating study/trial investigator is considered the principal investigator. The principal investigator for the local site, i.e., TMH, is considered the intramural principal investigator. The intramural principal investigator retains all responsibilities of a principal investigator. This distinction is made to facilitate clarification of role/relationship to the study.

Section 9

Investigator Noncompliance

9.1 Investigator Noncompliance

Regardless of an investigator's intent, unapproved research involving human subjects places those subjects at an unacceptable risk. Non-compliance is a significant failure by an investigator to abide by the IRB and federal regulations protecting human subjects of research. Non-compliance includes:

1. Beginning research before securing IRB approval;
2. Misuse or non-use of approved informed consent documents;
3. Failure to secure IRB approval for changes in an on-going protocol;
4. Continuing to gather data from subjects after IRB approval expires.

9.2 IRB Response

The IRB will take the following measures when investigator non-compliance is discovered:

1. The IRB will determine if human subjects may currently be exposed to harm or increased risk by the investigator's actions and if subjects may be harmed by halting the study. If potential harm exists, the investigator will be contacted and the study will be stopped temporarily;
2. The investigator will be notified that possible non-compliance has been observed or reported. The investigator will be asked for an immediate written statement explaining the situation;
3. After reviewing the investigator's statement, the IRB will determine whether further investigation is warranted. If further investigation is needed, the investigator will be notified that non-compliance review has begun, and that additional materials should be provided to the IRB;

If the IRB finds non-compliance, it will determine if subjects have been harmed or put at increased risk or if the non-compliance was deliberate.

Non-compliance is considered serious. The IRB will report to any supporting Agency or Department head (as appropriate) and OHRP/FDA within 30 days when it is required to do so. The investigator will be required to correct all problems and resubmit the protocol to the IRB for approval before continuing the study.

Investigators may appeal or ask the IRB for reconsideration of findings of serious non-compliance. These mechanisms must not threaten the independence of the IRB. Any serious or continuing non-compliance with 45 CFR part 46 or Title 21 the requirements or determinations of the IRB and any suspension or termination of IRB approval shall be promptly reported to the study sponsor, the Institutional Official, any government Department or Agency and OHRP as may be appropriate or required.

Section 10

Informed Consent

10.1 Informed Consent of Human Subjects of Research

Respect for persons requires that research subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. The informed consent process is the instrument to provide this opportunity. Except when a waiver is granted, the IRB requires that the investigators of a research project obtain informed consent from human subjects or their legally authorized representative at the time of consent. A legally authorized representative is defined as parent/s of a minor child; court appointed guardian; or Durable Power of Attorney (DPA) with specific instruction for research.

Informed consent is not valid unless the subject or the subject's legally authorized representative is fully informed about all the information in the consent document. Signatures on consent forms do not absolve the investigator of the responsibility to make sure that the subject or the subject's legally authorized representative is fully informed about the research. Signatures on the consent form should be the culmination of the initial consent process.

Once a subject agrees to participate, the subject or the subject's legally authorized representative must initial, sign and date the consent form in the appropriate places. The person obtaining consent must also sign, date and time the form and, in so doing, affirm that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives their consent to participate in the study. The person obtaining consent should sign the consent form on the date that he/she has actually performed the consent process.

10.2 Informational Component of Informed Consent

The IRB requires that the information necessary to give informed consent by the research subject is given to that person or the person's authorized representative in writing and orally. See the Consent for Research Template for guidance in developing a consent

1. The written document shall include the title of the study, the names of the investigators, and how the investigators may be reached;

2. The name of the Administrative Liaison/IRB and how he/she may be reached**;**

3. The content shall include at least the basic elements of informed consent; the use of a template or checklist prepared by the IRB is strongly recommended. In most instances, a single document shall be employed, encompassing all aspects of the research; the information shall not be fragmented;

4. The content shall be easily understandable by a layperson with modest education;

5. The investigator shall present the written document to the subject or the subject's authorized representative, and provide an opportunity and sufficient time for them to study the document and ask questions;

6. At the time of obtaining the consent, the investigator shall provide additional verbal information, as needed, so that the nature and anticipated consequences of the study are sufficiently clear;

7. In addition to the information given to the subject or the subject's authorized representative, the written document shall indicate that informed consent has been obtained prior to initiation of any study procedure. A third person must witness the consent interview only in the unusual situation that the subject or subject’s representative is not given the opportunity to read the consent document before it is signed. The witness will attest to the accuracy of the presentation and the apparent understanding of the subject.

8. Investigators will obtain the permission of one or both of the parents or guardian (as appropriate) and the assent of children or decisionally impaired individuals who possess the intellectual and emotional ability to comprehend the concepts involved.

Before the study may start, the text of the informed consent document must be approved by the IRB. Each copy of the document to be presented to the subject of research shall contain a "Date of Approval" corresponding to the date of the initial approval of the project by the IRB or the date that the informed consent was modified and approved by the IRB.

The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, an authorized representative of the subject, or if such a representative is not reasonably

available, a family member. This information will include the subject's participation in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, an authorized representative of the subject, or if such a representative is not reasonably available, a family member that s/he may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If an authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before an authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's authorized representative or family member, if feasible.

10.3 Exculpatory Language in Informed Consent Documents

In general, exculpatory language relates to the releasing of liability or fault for wrongful acts**.** Federal policy provides that no informed consent**,** whether written or oral, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights or releases the investigator, the sponsor, the institution or its agents from liability for negligence.

10.4 Obtaining Informed Consent

The process of obtaining informed consent has two components:

1. Providing the information necessary to give informed consent to the person who is being recruited to become a subject of research, or that person's authorized representative, and obtaining the consent to participate in the research as a subject;

2. Documentation that informed consent has been obtained to include consent to release Protected Health Information (PHI) as may be necessary. Except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent approved by the IRB and signed, dated and timed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

Except as provided in 21CFR 56.109(c), the consent form may be either of the following:

A written consent document that embodies the elements of the informed consent required by 21CFR 50.25. This form may be read to the subject or the subjects legally authorized representative, but, in the event the investigator shall give either the subject of the representative adequate opportunity to read it before it is signed; or

A short form written consent document stating that the elements of the informed consent required by 21 CFR 50.25 have been presented orally to the subject of the subjects legally authorized representative. When this method is used, there shall be a

witness to the oral presentation. Also, the IRB will approve a written summary of what is to be said to the subject or the representative

Informed consent must also be obtained prior to invasive procedures that are performed solely to determine eligibility for research.

Consent is an ongoing process that requires the investigator to keep subjects apprised of issues that arise which may affect their willingness to continue participation. The subject's continued willingness should be documented periodically in the subject's medical record and/or research record, and in some cases a revised consent form or addendum may be appropriate.

10.5 Persons Authorized to Obtain Informed Consent from Research Participants

Informed consent for research shall be obtained by the principal investigator or designee who is who familiar with all aspects of the research protocol and is listed on the Application for Approval of Research Involving Human Subjects as a research investigator or co-investigator.

The person obtaining consent must sign the form. By so doing, he/she attests that the subject has been fully informed about all aspects of the study, alternatives to participation have been discussed, and the subject willingly gives her/his consent to participate in the study.

10.6 Documentation of Obtaining Informed Consent

In most instances, the act of obtaining consent is validated when the subject or the subject's authorized representative and the investigator or authorized designee sign the written informed consent. In the case of a child/decisionally impaired individual able to comprehend the nature, risks and benefits of the research study a signature assenting to participate in the study is required in addition to the signature of the authorized representative.

Cases involving a short form written consent, only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to the copy of the short form.

One copy of the signed consent form must be given to the person signing the consent form (subject or representative) and a second copy should be placed in the subject's medical chart when the study patient is receiving study treatment in the hospital or TMH outpatient setting. The original, signed consent form must be retained in the PI's research records. Consent forms must be retained for all subjects enrolled in the study, regardless of whether they withdraw or are withdrawn. Subjects are considered enrolled at the moment they sign the consent form, whether or not they actually participate in the research or any of the procedures involved.

The following information should be documented in the subject's record of all patients in studies involving medications / devices:

1. A statement in the progress note for the professional domain of the investigator/study coordinator obtaining the informed consent that the subject met all inclusion/exclusion criteria;
2. The consent was discussed explaining procedures and requirements, viable alternatives and material risks, if any;
3. The subject was given an opportunity to ask questions and receive answers;
4. The consent was obtained prior to any study procedures;
5. The subject was enrolled in study “Title” and given a copy of the consent; and
6. The note includes a signature, date and time.

10.7 Waiver of Informed Consent Requirements

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent in instances where the IRB finds and documents that certain criteria (as listed below) are met. IRB Form 4b must be completed when requesting a waiver of the informed consent requirement. The IRB may decide not to grant a waiver, and to require all of the elements of consent, for protocols which appear to meet these criteria if it determines that doing so is in the best interest of the subjects.

A complete waiver of informed consent can only be granted if one of the two following sets of criteria is met:

Criteria 1

- The research or demonstration project is to be conducted by or is subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in methods or levels of payment for benefits or services under those programs; and
- The research could not practicably be carried out without the waiver or alteration.

Criteria 2

- The research involves no more than minimal risk to the subject;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The research could not practicably be carried out without the waiver or alteration.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation; and
- the criteria are met for a waiver of HIPAA authorization to use or disclose PHI in the conduct of research.

10.8 Re-consenting Subjects

Subjects may need to be re-consented due to changes in their status (i.e., previously enrolled by proxy and are now able to consent on their own behalf) or due to changes in the protocol and/or consent form as follows:

1. The protocol and/or consent form has been modified since the subject enrolled and the changes are more than administrative (i.e., the information which has been added/deleted may have an impact on risk to subjects and their willingness to participate).
2. The subject was initially enrolled in a study by parents, a legally authorized representative or a research proxy because the subject was a minor at the time of entry into a study and has since reached the age of 18 and can now consent on his/her own behalf, or the subject was incapacitated at the time of enrollment and has regained capacity to consent on his/her own behalf.

Regarding subjects asked to re-consent due to modifications to the consent form and/or protocol:

1. If the modifications are minor, it may be appropriate to provide the subject with an addendum to the original consent form that provides the new information, or to verbally inform subjects of an administrative or other minor change with documentation in the medical record that such notification took place.

2. If an addendum is used, it must clearly state that the information in the original consent form is still current and valid, and that the information is the addendum is supplementary.

In the event substantive modifications to the consent form are recommended by the central IRB – i.e., modifications affecting the rights, safety, or welfare of the subjects – the principal investigator will report those recommendations to the TMH IRB. If the modifications are major, subjects must be given a completely revised consent form to sign.

10.9 Projects Eligible for Waiver or Alteration of the Informed Consent Process in Non-Emergency Situations

The FDA does not recognize the waiver of informed consent in non-emergent situations (21 CFR 50.24, and 21 CFR Parts 56, 312, 314, 601, 812, and 814). Consistent with 45 CFR 46.117(c), the IRB may waive the requirement for the investigator to obtain a signed consent form from some or all subjects of research, if the IRB finds and documents that:

1. It s not violative and not invasive;
2. It does not involve risks to the subjects that are more than minimal; minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests;
3. It does not adversely affect the rights and welfare of the subjects;
4. It does not reveal subjects' identity, placing them at risk of criminal or civil liability, or damaging their financial standing, employability or reputation;
5. It does not involve the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens, in such a way that the subjects can be identified directly or through identifiers linked to the subjects;

6. The Waiver of HIPAA Authorization Notification Request (IRB Form 4c) was approved;
7. The only record linking the subject and the research is the consent document and the principal risk would be potential harm resulting from a breach of confidentiality;

Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern;

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

10.10 Waiver of Informed Consent in Emergency Research

The IRB may consider granting a waiver to the requirement for obtaining and documenting informed consent from a person or his/her authorized representative, as a condition of becoming a subject in a research project, in the following circumstances:

1. The person being considered as a research subject is facing a life-threatening condition that requires emergent action to save life, available treatments are unproven or unsatisfactory and the collection of valid and scientific evidence, which may include evidence obtained through randomized placebo controlled investigations, is necessary to determine the safety and effectiveness of the particular intervention.
2. The person facing the life threatening, emergent condition is not capable of giving informed consent as a result of the condition; and
3. An authorized representative, who could give informed consent on behalf of the person facing the life-threatening condition, is not accompanying the person and is not readily accessible within a therapeutic window of time;
4. There is not time enough to locate an authorized representative to obtain consent.
5. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.
6. Participation in the research holds out the prospect of direct health benefit to the subject.

When FDA regulated products are involved (drugs, biological products, and medical devices), the Federal Regulations 21 CFR 50.24, and 21 CFR Parts 56, 312, 314, 601, 812, and 814 are those used by the IRB to determine if a waiver is applicable.

The IRB reviews and approves the emergency consent procedures and documents.

Additional protections for study participants involved in emergency research may include:

1. Consultation with community representatives;
2. Public disclosure of plans, risks and benefits;
3. Public disclosure of study results;
4. Involvement of an Independent Data Monitoring Committee; and

5. Summarized family members' objections as a part of continuing review.

The IRB is responsible for ensuring that procedures are in place to inform each subject / authorized representative at the earliest feasible opportunity of the subject's inclusion or discontinuation in the clinical investigation. In addition, there should be procedures to inform the family, if the subject dies.

Section 11

Vulnerable Populations and Decisionally Impaired Individuals

11.1 Vulnerable Populations:

Vulnerable populations include: children, fetuses, pregnant women and prisoners. Decisionally impaired individuals and TMH colleagues also require special IRB considerations

11.2 Persons Authorized to Give Permission for a Subject (other than themselves) to Participate in Research

Consent, or agreement to participate in a research study, shall be given by the individual who will be the research subject or a person who is permitted to act on behalf of that individual (a legally authorized representative). For adult subjects incapable of consenting to participation due to their clinical or mental condition, the IRB may approve a process whereby permission may be obtained from the subject's legally authorized representative or, in limited cases, next of kin.

For children, the parent or legal guardian shall be permitted to act on behalf of the child and give permission for their participation. However, the assent of the child shall be obtained from any child considered mature enough to understand (usually in the range of 7-9 years of age), unless the IRB determines that the assent requirement can be waived (see Waiver of the Assent Requirement). The FDA regulations do not specifically address enrollment of children (other than to include them as a class of vulnerable subjects); therefore, the basic requirements under 21 CFR 50.20 applies.

All research involving children as subjects shall be placed into one of the four categories of risk as outlined at 45 CFR 46.404, 405, 406, 407. The categories are as follows:

1. Research not involving more than minimal risk. 46.404
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. 46.405
3. Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. 46.406

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (Approval of research included under this category is very rare). 46.407. Research in this category needs approval of the Secretary – DHHS in addition to IRB approval.

In compliance with 45 CFR 46.408, when research is covered under the first or second bullet above (45 CFR 46.404 or 45 CFR 46.405), the permission of one parent shall be considered adequate unless the IRB indicates otherwise in its approval letter.

Where research is covered under the third or fourth item above (45 CFR 46.406 or 45 CFR 46.407, and when permission is to be obtained from parents, both parents shall give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. In this case, when only one parent is giving permission, the justification for not requiring the other parent's signature shall be documented in the research record and on the consent form.

11.3 Research with Decisionally Impaired Adults / Minors

Federal recommendations include the requirement to obtain assent from individuals who do not have the capacity to provide consent for themselves. This may be due to a condition that renders them permanently incapable of consenting, or a temporary condition that makes it impossible to obtain their informed consent at the time that enrollment must occur.

Assent is not just a form; it is a process involving a discussion between the investigator and the decisionally impaired adult. While the assent form example may be used verbatim, investigators should consider whether certain sensitive information, such as requirements for pregnancy or drug testing, should be conveyed in writing. In addition, investigators should list any study requirements the decisionally impaired adult must perform on her/his own, such as keeping a diary, monitoring activity levels, etc.

If a subject regains his/her ability to make healthcare decisions, s/he should be given the opportunity to provide consent. (See Section on Re-consenting Subjects)

11.4 Waiver of the Assent Requirement

The IRB may grant a waiver for the assent requirement when it is determined that there is a prospect of direct benefit, no standard approved therapy exists which is equally effective, and/or the child / decisionally impaired may not have the ability to understand the ramifications of not participating.

11.5 Board Responsibilities

Any project that involves interaction or intervention with subjects considered to be vulnerable must be reviewed by a convened meeting of the full Board regardless of the risk.

The IRB will consider research projects involving vulnerable populations if one of the following conditions is met:

1. The research does not involve more than minimal risk to the subject.
2. The research is likely to benefit the subject directly, even if the risks are considered to be more than minimal.

Requests for approval of any research that exposes vulnerable populations to risks significantly greater than minimal, without providing obvious direct benefit to the subject, will have to be submitted to the United States Secretary of Health and Human Services for review and approval.
The IRB will not review or approve any research involving prisoners, unless it has already been approved by another accredited institutional review board that has a prisoner consultant.

Section 12

Conflict of Interest

12.1 Investigator Conflict of Interest

The IRB considers that the most important step in managing potential conflicts of interest lies in appropriate disclosure, and this begins with the investigator disclosure to a sponsor and the IRB of financial holdings, relationships, and other interests which might constitute a conflict of interest for the researcher as an investigator.

An investigator has a conflict of interest when that individual has any financial interest in which the value could be affected by the outcome of the research, or non-financial interest or any personal or professional relationship or reason, which may make it difficult for the individual to exercise independent judgment in safeguarding the rights and welfare of human research subjects

A financial conflict of interest is not intrinsically wrong. Rather, the purpose in analyzing a financial conflict of interest is in trying to determine when the interest offers incentive to the investigators or other party to breach a duty to subjects or to society, and how to address the conflict of interest. As individuals vary in their personal integrity, and as the IRB generally does not know investigators and other parties intimately enough to judge their integrity, the IRB refers these instances to the TMH Corporate Compliance Officer for review and recommendation.

12.2 Evaluating Conflicts of Interest

Based on the recommendations of the Corporate Compliance Officer, the IRB may take the following actions:

1. A finding that the conflict of interest is not likely to jeopardize subject safety or bias the investigator's decision-making and does not require further action.

2. A finding that disclosure of the conflict to subjects or others is necessary.
3. A finding that controls on the conflict need to be put into place, such as limiting the role of the investigator with a conflict of interest.
4. A finding that the conflict is unacceptable, and must be eliminated in order for the research to precede.

Section 13

Research and HIPAA (Health Insurance Portability and Accountability Act of 1996) Privacy Rule Compliance

An individual's protected health information (PHI) may only be used for research after the investigator has obtained the approval of the IRB. Where the Privacy Rule, the Common Rule, and/or the FDA's human subject regulations are applicable, each set of requirements must be met. When there is a difference in the requirements, the highest level of protection shall be followed. The IRB shall serve as the "Privacy Board" for research.

The full text of the HIPAA regulations is available at: http://www.hhs.gov/ocr/hipaa.

The Health Insurance Portability and Accountability Act (HIPAA) is federal legislation designed to enable a person to go from one health insurance plan to another with continuity of care and to ensure that he/she will not be denied coverage for a "pre-existing condition" (portability); it details government oversight to protect fraud and finally adds protections for confidentiality of protected health information (PHI) that is collected (accountability).

13.1 Protected Health Information

Protected health information (PHI) is individually identifiable health information that is collected for treatment, diagnosis or research purposes. HIPAA details eighteen items that render PHI identifiable:

1. Names
2. Geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code in certain situations.
3. All elements of date (except year) for dates directly related to an individual, including birth date, discharge data, date of death; and all ages over 89 and all elements of dates indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social security numbers

8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers
13. Medical Device Identifiers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code.

13.2 Research Categories under HIPAA

There are three categories of research data to be considered under HIPAA:

1. Identifiable information (to which the rule applies) See TMH HIPAA Privacy Program Policy 30, Use and Disclosure of PHI for Research Activities. https://intranet.tmh.org/policies/HIPAA/documents/30-UseandDisclosureofPHIforResearch.pdf
2. De-identified information (to which the rule **does not apply**) See TMH HIPAA Privacy Program Policy 26, De-identification of Protected health Information https://intranet.tmh.org/policies/HIPAA/documents/De-Identification%20of%20PHI.pdf
3. Limited data set (a middle option, to which limited parts of the rule apply) See TMH HIPAA Privacy Program Policy 26A , Limited Data Sets https://intranet.tmh.org/policies/HIPAA/documents/Limited%20Data%20Sets.pdf

13.3 Data Use Agreement

A data use agreement (IRB Form DU) is an agreement into which the covered entity enters with the intended recipient of a limited data set that generally describes the permitted uses and disclosures of the PHI in a limited data set and how the data will be protected.

If an investigator plans to use a limited data set for research, s/he must submit a data use agreement with her/his IRB protocol submission.

13.4 Minimum Necessary Standard

HIPAA also requires that researchers comply with a “minimum necessary standard”. This means that a research protocol must limit the PHI it uses, discloses, or requests to the minimum necessary to achieve that purpose. The standard applies to all research involving the use of PHI, including protocols involving the use of a limited data set and/or a waiver of authorization, and for reviews preparatory to research. See TMH HIPAA Privacy Program Policy 28, Minimum Necessary Standard https://intranet.tmh.org/policies/HIPAA/documents/MINIMUM_NECESSARY.pdf

13.5 Authorization from the Research Subject

Authorization is a person's signed permission allowing a covered entity to use or disclose that person's PHI as specified for a specific purpose – current research or specified future research – as outlined in the authorization form. There are important differences between Privacy Rule requirements for individual authorization, and Common Rule and FDA requirements for informed consent (See Informed Consent). HIPAA requires more specific details about all possible uses – the sharing of PHI within the covered entity - and disclosures - the sharing of PHI outside the covered entity of PHI

The information required under HIPAA for authorization may be incorporated into the research consent form. (See Compound Authorization). Therefore, a subject may provide consent and authorization together as part of the informed consent process, if determined by the IRB to be appropriate. See TMH HIPAA Privacy Program Policy 22, Authorization for Uses and Disclosures of Protected Health Information. https://intranet.tmh.org/policies/HIPAA/documents/Authorization_Policy.pdf

13.6 Individual Rights

Under HIPAA, individuals have the right to:

1 **Access their PHI:** The individual may request a copy or the opportunity to inspect the PHI that has been utilized as part of the research study. This access is limited to a "designated record set" which includes PHI that is used to make clinical or billing decisions about a subject. In order to prevent the compromise of research data, access can be postponed until the research is complete, as long as this is clearly explained in the authorization (or research consent form). See TMH HIPAA Privacy Program Policy 17, Patients Right to Access Protected Health Information
https://intranet.tmh.org/policies/HIPAA/documents/RIGHT_TO_ACCESS.pdf

2. **Request amendment to their PHI:** The individual has the right to request an amendment to their PHI. The institution will determine whether or not the request is appropriate.

3. **Receive a record of certain disclosures of their PHI made within the previous 6 years:** This does not apply to disclosures that were made pursuant to an authorization, or disclosure of a limited data set. Individuals may request a record of disclosures made under a waiver of authorization or disclosures required by law and for public health purposes. Therefore, any such disclosures must be tracked. See TMH HIPAA Privacy Program Policy 21, Accounting and Tracking Disclosures of Protected Health Information https://intranet.tmh.org/policies/HIPAA/documents/Accounting_and_Tracking_Disclosures.pdf

4. **Request restrictions on uses and disclosures:** Individuals can request certain restrictions on uses and/or disclosures of their PHI, if it is determined that the request is appropriate and feasible. See TMH HIPAA Privacy Program Policy 20,

Patients Right to Request Restrictions on the Use and Disclosure of Protected Health Information
https://intranet.tmh.org/policies/HIPAA/documents/request_restriction.pdf

5. **Request receipt of communication of their PHI by alternative means / location:** An individual may request, for example, that a different address be used to communicate information (home vs. work). Reasonable request must be accommodated, and the individual does not have to explain the basis for the request.

6. **Revoke their authorization:** A revocation of authorization must be made in writing. If research authorization is revoked, PHI may no longer be used or disclosed, except to the extent that the PHI has already been included in study analyses, or if the use or disclosure is needed to maintain the integrity of the research study (i.e. account for withdrawal, report adverse event, etc.).

13.7 Waiver of Authorization

There are situations in which the IRB may waive the requirement that subjects sign an authorization form. In general, a Waiver of Authorization could be granted under similar circumstances that the IRB grants a Waiver of Informed Consent (e.g., for retrospective chart reviews, etc.).

Any study granted a waiver of informed consent and approved by the IRB must also have a Waiver of Authorization. A Waiver of Authorization does not mean the research is exempt from HIPAA privacy rules. It only means the investigator does not need to obtain signed authorization from each research subject.

In order to qualify for a Waiver of Authorization, an investigator must represent the following:

1. The use of PHI for research does not represent more than a minimal risk to privacy.
2. The research could not be done without the requested PHI.
3. It would not be practical to obtain signed authorization from research subjects.
4. The specific elements of the requested health information are not more than the minimum necessary to conduct the study.

13.8 Partial Waiver of Authorization

There are circumstances that would require a PI to obtain a partial waiver (or alteration) of authorization. See “Recruitment of Study Subjects.”

13.9 Compound Authorization

As of January 25, 2013, the HIPAA Omnibus Rule amended 45 CFR 164.508(b) (3) (i) and (iii) to allow a covered entity to use compound authorizations for conditioned and unconditioned research activities. Specifically, the Privacy Rule now permits an authorization for the use or disclosure of PHI for a research study to be combined with any other type of written permission for the same or another research study, including

combining such an authorization with an authorization for the creation/maintenance of a research database or repository or with a consent to participate in research. If a health care provider has conditioned research-related treatment on the provision of one of the authorizations (as permitted by the Privacy Rule), then any such "compound authorization" is required to differentiate clearly between the conditioned and unconditioned research components and also must allow the subject the option to opt-in to the unconditioned research activities. Therefore, the subject must affirmatively authorize unconditioned research activities and specifically addressed scenarios involving revocation of compound authorizations.

The HIPAA Omnibus Rule's modifications to 45 CFR 164.508(b) (3) (i) and (iii) permit, but do not require, covered entities to create compound authorizations for conditioned and unconditioned research activities. Thus, ongoing studies that were previously approved can continue to rely on the separate authorizations previously obtained. New research studies may choose to use separate authorizations for conditioned and unconditioned research activities or can move to using compound authorizations as described in the HIPAA Omnibus Rule.

Section 14

Honest Broker

14.1 Honest Broker Process

Health information may be used or disclosed without patient authorization when the information or data are de-identified in accordance with the Privacy Rule. The honest broker process assures that all data identified or disclosed to include PHI is in accordance with applicable regulations and the research protocol approved by the TMH IRB.

An honest broker is an individual, acting on behalf of TMH, who collects and provides clinical data for researchers. This is done through the use of automated tools and manual screening to ensure PHI are removed from the data and replaced with unique identifying codes, when necessary. The honest broker is assigned by the VP / Organizational Improvement and Planning; and all data transactions must be through the VP / Organizational Improvement and Planning.

14.2 Honest Broker Selection Criteria

For an individual to be an honest broker at TMH, the individual must meet the following criteria:

1. The applicant must be a TMH employee, contract staff (assigned an employee number beginning with N) or credentialed associate and not a part of the study or research team.
2. The individual must be proficient in the use of the TMH's medical record systems.

3. The individual must submit an approved application to become a TMH honest broker. The application is available on the TMH IRB website and should be submitted to the VP / Organizational Improvement and Planning who will approve the application and supervise the activity of data abstraction.
4. The honest broker applicant must complete the identified readings (HIPAA and related TMH Privacy and Security policies), education and test.
5. All honest brokers must provide a written statement assuring that they will abide by all relevant federal regulations and TMH HIPAA Privacy and Security policies and procedures.

Section 15

Recruitment of Study Subjects

The IRB shall review and approve, prior to utilization, all documents and activities that affect the rights and welfare of research subjects, including all methods and materials intended to recruit human subjects.

15.1 Recruitment Mechanisms

The mechanism for recruitment must be described by the PI in the protocol and submitted to the IRB for approval before implementation. Potential subjects may be recruited by one of two mechanisms.

15.1.1 Recruitment by Clinician or Treatment Staff

A clinician, **who is also a researcher**, may approach a patient he/she is currently treating about participating in any IRB approved study for which that clinician is conducting research. The clinician's treatment personnel (who already have access to a patient's identifiable health information by virtue of the treatment relationship) may also approach the patient about participating in research. The clinician and the treatment staff must note any such communication in the patient's medical record. The following items are suggested:

1. A statement in the progress note for the professional domain of the investigator/study coordinator obtaining the informed consent that the subject met all inclusion/exclusion criteria;
2. The consent was discussed explaining procedures and requirements, viable alternatives and material risks, if any;
3. The subject was given an opportunity to ask questions and receive answers;
4. The consent was obtained prior to any study procedures;
5. The subject was enrolled in study "Title" and given a copy of the consent; and
6. The note includes a signature, date and time.

The IRB must grant a partial waiver of HIPAA authorization and screening/recruitment request for a clinician/researcher or his/her treatment staff to review patient files for prospective study subjects or retrospective studies.

A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may approach a patient about participating in another researcher's study. The clinician or staff should note such communication in the patient's medical record. If the patient agrees to be referred to the researcher, the following language is suggested:

- I discussed the possibility of referring the patient to [doctor or team] for [describe research study]. The patient agreed to the referral and to sharing information about his/her condition with the researcher.

A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may give the patient another researcher's name and contact information. The patient may then choose to contact that researcher directly.

A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may discuss a patient's eligibility with the research personnel as long as all information about the patient has been de-identified. If the research personnel think the de-identified patient would be eligible for the study, the treatment personnel could then obtain the patient's permission to give the research personnel the patient' name or give the patient the researcher's contact information

A clinician, **who is NOT the researcher**, and that clinician's treatment staff, may send a letter to the patient about how to join an IRB approved study as long as the content of the letter is approved by the IRB. Unless the IRB approves a waiver of authorization for study recruitment purposes, the letter may NOT be co-signed by the researcher and the researcher may not have a copy of the letter.

15.1.2 Recruitment by the Researcher If the treating clinician's direct approach to the patient (the patient is not currently being treated) or the patient's prior authorization is impracticable, the researcher may ask the IRB to grant a partial waiver of the patient's authorization for recruitment purposes.

A partial waiver of authorization may be requested for the following:

1. To allow treatment staff to refer patients to the researcher or to share PHI with the researcher without first speaking to the patient about the referral.

2. To advertise about the study and screen by phone potential subjects for the study.

3. To screen medical records for prospective subjects from clinician's patient population currently being treated.

15.2 Recruitment Methods

Potential subjects may be recruited for research studies using a variety of methods, including direct contact (where appropriate), advertising, chart reviews, database review, or other written/verbal correspondence. All of these methods must be consistent with federal regulations regarding the rights and welfare of potential subjects

(Common Rule Requirements), the Privacy rule (HIPAA Privacy Rule Requirements), and Institutional policies.

15.2.1 Using Letters to Contact Potential Research Participants In most cases, contacting potential research subjects by letter will occur only when that subject is familiar with the person writing the letter. If personal information about the subject is necessary in order to identify the subject as a potential participant (such as having a certain disease or clinical condition), then the contact shall come from a person that the subject would expect to have that information (e.g., personal physician, a disease-related organization to which the subject belongs, etc.).

Any letter that is sent to a potential research participant is subject to the same requirements as advertising, and must contain no coercive language. The letter should briefly explain the study, its purpose, and the reason why the person is being asked to participate. There should be a mechanism by which the person can express an interest (by calling her/his physician or a researcher, sending back a card, etc.). Failure to respond should never be construed as a willingness to participate. It should be clearly stated if a follow-up phone call is to come from the person who wrote the letter. It must also be clearly stated that participation is voluntary, and the subject has the right to refuse to participate without any loss of benefit to which s/he would otherwise be entitled. If possible, a consent form should be included, and a phone number where the person can direct questions about the study should be provided.

15.2.2 Advertising No advertising material may be used prior to approval by the IRB. The IRB shall review all printed media advertisements, internet advertisements (which include more information than simply a listing of available trials), scripts of radio and television commercials, flyers, postcards, letters, pamphlets, brochures, videos, and any other advertising material proposed for use in recruiting study subjects.

The investigator should submit the advertisements, scripts, etc. with the initial submission packet (for new submissions) or IRB Form 8a (for approved studies) to the IRB for approval prior to utilization.

All materials to be utilized for recruitment via the mass media (print media such as newspapers or television and/or radio air time) shall be developed in conjunction with the TMH Public Relations (PR) Department. The PR Department will assure that the materials are designed and presented in accordance with TMH guidelines.

Once approved by PR, the investigator should submit the advertisements, scripts, etc. with the initial submission packet (for new submissions) or IRB Form 8a (for approved studies) to the IRB for approval prior to utilization. No “open reads” for radio or television are permitted. Open reads are live discussions by a person on radio or television that are intended as advertisements. For example, when a radio host talks about how great a particular store is, and you are led to believe that it is his personal opinion when, in fact, he is reading or acting out an advertising script.

See the following guidance provided by FDA for Media Advertising:
http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting

The IRB uses the principles set forth in this FDA guidance when reviewing advertising materials for clinical trials and other studies that advertise for potential subjects.

Advertisements should:

1. make no claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or;
2. make no claims, either explicitly or implicitly, that a test article is known to be equivalent or superior to any other drug, biologic or device;
3. not use terms such as "new treatment," "new medication" or "new drug;"
4. not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation;
5. limit the information to the prospective subjects to that needed to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. Not all items may be necessary;

    - the name and address of the clinical investigator and/or research facility;
    - the condition under study and/or the purpose of the research;
    - in summary form, the criteria that will be used to determine eligibility for the study;
    - a brief list of participation benefits, if any (e.g., a no-cost health examination);
    - the time or other commitment required of the subjects;
    - the location of the research and the person or office to contact for further information;
    - State only that the subjects are paid and not the amount paid.

15.2.3 Recruitment on the Internet Recruitment of research subjects via the internet must be approved by the IRB before implementation. Recruitment plans will be reviewed and evaluated in accordance with the basic principles governing human subject protections.

15.3 Recruitment Incentives and Conflict of Interest

It is against the policy of the TMH for an employee to solicit or accept gratuities from patients, their families or friends for any services provided by the employee during work hours, or for any member of the employee's immediate family to accept gifts, gratuities, or entertainment that might influence the employee's judgment or actions concerning business of TMH. For employees involved in research, this includes any payment from study sponsors above and beyond payment that has been approved in the study budget. Budgets that include bonuses for recruitment or other activities are never allowed.

15.4. Payment to Research Participants

The IRB reviews and approves payments to human research participants as part of the initial and continuing review of the study protocol and informed consent.

15.4.1 Disclosure of Payments All information concerning payment, including the amount and schedule should be described in the informed consent document.

15.4.2 Advertisement of Payments Advertisements may state that participants will be paid or compensated, but should not emphasize the payment or amount to be paid.

15.4.3 Alterations in Payments Any alterations in research participant payment or liberalization of the payment schedule must be submitted as a modification (IRB Form 8a) to the IRB for approval prior to implementation.

Section 16

Application Process

16.1 Overview

In order for a protocol to be placed on the IRB meeting agenda, it shall be submitted on or before the deadline date and conform to all of the requirements. If the submission is incomplete (does not conform to all requirements.), the Office of Research/IRB shall notify the principal investigator (PI) / research coordinator of the deficiencies and/or return the submission to the PI/research coordinator. There must be one PI who has overall responsibility for the study; all others are co-investigators or sub-investigators.

In addition to the designation of a PI, research protocols submitted for IRB review must list all co-investigators who will be involved in the research; only those individuals listed may recruit subjects and participate in the study. An investigator may not participate in research until he/she has provided evidence of completion of basic research education or provided an acceptable equivalent. Based on current regulatory requirements, the IRB may mandate additional education prior to an individual's involvement in research. If the protocol involves a special area of investigation, including radioisotopes (i.e., x-rays, CT Scans, PET Scans, Radiation Therapy, etc.,), biohazards, nursing participation or investigational drugs, approval from the appropriate individuals with oversight responsibility in these areas is required.

If the research involves recruitment of subjects from physicians that are not in the PI's practice, authorization from the physician to contact the subjects is required prior to approaching the potential study participant.

16.2 Electronic Submission Process

The TMH IRB uses *Iris,* a web-based application to process all research documents. Prior to starting the electronic submission process, a user name and password must be obtained. This can be done by contacting the IRB Office.

All study processes can then be completed by accessing:

https://tmh.imedris.net/Login

Detailed instructions and resources are available on the TMH IRB wed site.

Section 17

IRB Actions and Decisions

After a research protocol has been reviewed, the Office of the IRB will send written notification to the PI with one of the following decisions:

17.1 Approval

Approved as submitted with no modifications required. The approval letter will include the date that the first progress report is due as determined by the IRB and any other conditions that apply.

17.2 Contingent Approval

Protocol requires minor revisions that do not affect the safety of the research subject. The IRB Chair/designee may approve the study upon receipt of the satisfactory revisions without further review by the convened IRB. If no revisions are received by the IRB within 120 days, the protocol will be withdrawn from consideration.

17.3 Tabled

Substantive issues regarding the protocol and/or consent form must be addressed. The investigator's response to initial review requests must be reviewed by the IRB at a convened meeting. If the PI does not respond within 120 days, the protocol will be withdrawn from consideration.

17.4 Disapproval

Questions are of such significance that the IRB feels approval of the study to be unwarranted. Review of a previously disapproved protocol that has been revised and resubmitted requires full-board review.

17.5 Protocol Suspension

An action taken by the Chair / Board to temporarily stop some previously approved research activities, typically taken "for cause." Protocols may be suspended for:

1. Non-compliance
2. Unanticipated problems involving risks to subjects
3. Study expiration
4. By request of the PI / sponsor

17.6 Protocol Termination

An action taken by Chair / Board to permanently stop all activities of an approved research protocol. Terminated protocols are considered closed and require a final report from the PI.

The following are two different mechanisms by which a protocol may be terminated:

- **Voluntary termination** by the investigator or sponsor (study ends, investigator leaves the institution, etc.). If a study is voluntarily terminated, the PI must notify the IRB by completing and submitting a Termination Report IRB Form 9. The IRB will accept the termination report, place it with the study file and close the study. No formal written acknowledgement of the termination of a study to the PI or sponsor will be provided unless requested

- **Administrative termination** by the IRB due to safety concerns, investigator non-compliance, or delinquent progress reports (failure to renew a protocol prior to expiration of IRB approval). If a protocol is administratively terminated, the IRB Chair/designee will notify the PI in writing that the protocol has been terminated by stating the reason for the termination, i.e., due to delinquent progress reports, concern for safety of human subjects, non-compliance, etc. In a case of immediate hazard to subjects, initial notification may be in the form of a telephone call or e-mail from the IRB Chair or designee.

If a study approval is terminated:

1. Current participants must be notified
2. Procedures for withdrawal of enrolled subjects consider the rights and welfare of the subjects
3. When follow up of subjects for safety reasons is permitted / required by the IRB, any adverse events or outcomes should be reported to the IRB and the sponsor

17.7 The Appeal Process

A PI may appeal a decision made by the IRB within 120 days of the date of the decision letter from the IRB. The appeal must be made in writing and sent to the IRB Chair or Office of Research/IRB along with any supporting materials. The Chair and Office of Research/IRB will review the appeal and decide whether additional information is necessary to present at the IRB meeting. The appeal will be brought to the next convened meeting of the IRB. The Chair may invite the PI to attend the meeting to give a presentation of the protocol and to address problematic issues. Written notification of the IRB's decision of the appeal will be sent to the PI following the meeting.

A decision for disapproval after appeal is final. The final decision by the IRB may not be overturned, either by further appeal by the PI in writing, or appearing at a meeting of the IRB or by another institutional official. If significant modifications are made to a previously disapproved protocol it may be submitted as a new protocol. The IRB Chair has the authority to determine whether a previously disapproved protocol has been amended sufficiently to warrant review as a new protocol.

17.8 Other Activity as Determined by the IRB

The IRB has the authority to request additional information, as necessary, to assure patient safety and compliance with federal and state regulations and institutional policy ensuing research is conducted and evaluated in accordance with the basic principles governing human subject protections

17.9 Communication of Board Actions

Upon completion of the review of a research project application, the IRB staff will notify in writing the applicant principal investigator of the outcome of the review. This document will include the following information:

1. The outcome of the review by the IRB, and the date the decision was reached;
2. Modifications in the protocol required for approval;
3. For approved projects, the date of next scheduled Progress Report (expiration date of the approval), and the reporting requirements for the principal investigator;
4. For disapproved, suspended or terminated projects, the reasons for these decisions, and the rights of the investigators for rebuttal of the decision.

The primary investigator is responsible for conveying routine IRB decisions to the sponsor, other organizations and agencies. However, in the event of an adverse decision, the IRB will notify the sponsor, external agencies and other organizations.

Section 18

Central IRB Review Process

18.1 Approval Process

Tallahassee Memorial HealthCare, Inc. (TMH) may allow the approval and oversight of centralized review boards when multicenter trials are involved. However, prior to association with a central IRB, a formal agreement that delineates the responsibilities of both TMH and the central IRB must be approved and signed by TMH's IRB Liaison and the central IRB's designated representative. This agreement will be maintained in accordance with TMH's contract review policy.

Individual studies associated with a central IRB will be approved on a case by case basis after:

- TMH's Research Council and the Compliance Officer review the study protocol and associated study documents for feasibility.
- TMH's IRB Office staff reviews the associated study documents for completeness.
- The Chair or Vice Chair reviews the study's plan for the recruitment and informed consent processes, assuring consideration to community attitudes and cultural backgrounds. If the plan is acceptable, the application is approved through the exempt process.

18.2 TMH Responsibilities

However, even when a centralized review board is used, TMH maintains full responsibility for the conduct of the site specific study, as well as:

- HIPAA compliance (Honest Broker)
- Institutional consent language
- Data security
- Conflict of interest
- Institutional biosafety

18.3 Primary Investigator's Responsibilities

The principal investigator is responsible for compliance with TMH IRB guidelines, maintaining current and accurate protocol documentation and reporting adverse events in accordance with reporting requirements.

Section 19

Continuing Review of Ongoing IRB-Approved Research

The IRB shall conduct continuing review of all research activity in compliance with 45 CFR 46 and 21 CFR 56. Continuing review is required for all research protocols approved by the IRB at TMH (unless the protocol was categorized as "exempt" by the IRB at the time of submission) for the term of the research, as long as individually identifiable follow-up data are being collected or analyzed.

It is the responsibility of the principal investigator (PI) to comply with continuing review requirements. Continuing review includes, but is not limited to the following:

19.1 Progress Reports

According to federal regulations, a research protocol can only be approved for a maximum of 365 days. Within that time period, continuing review is conducted at intervals specified at the time of initial approval. Those intervals are based on the degree of risk to study subjects. If the risk/benefit ratio changes at any time during the study, the PI is obligated to notify the IRB; the IRB has the authority to modify the continuing review interval and/or request changes to the protocol. The IRB also has the authority to require additional information at any time or to request an audit of the research to assure the safety of subjects and compliance by the research team.

To renew the approval period, the PI must submit a progress report and any requested relevant documents to the IRB before the project's expiration (the date at which the current approval ends). Since the IRB does not have the authority to extend the

approval period beyond the expiration date, it is essential that the PI submit a complete progress report by the due date set by the IRB.

It is the PI's responsibility to comply with institutional policy and provide the IRB with the required progress report. As a courtesy, the IRB may provide a reminder to the PI to submit the progress report in advance of the project's expiration date. If the PI successfully complies with the progress report request by the due date set by the IRB, the study will be presented at the next convened IRB meeting prior to renewal.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. All research activities must cease and desist. Federal guidance indicates that short-term continuation of the research procedures beyond the IRB approval date may be permissible for the safety of enrolled research subjects that involve therapeutic intervention or interaction, if the investigator is actively pursuing renewal with the IRB; and the IRB believes that over-riding safety concerns or ethical issues are involved. There must be notification, in writing, to the Office of Research/IRB of all such situations, including a justification for interaction while the study is in the process of being re-activated. It is critically important that the investigator re-activate the protocol rapidly (see Re-activation of Terminated Protocol).

If a progress report is submitted and received prior to the expiration date but is deficient, the Office of Research/IRB will contact the PI/Research Coordinator with details regarding the deficiencies. If a complete and correct progress report is not received within the required time frame, the project is subject to the same termination procedures outlined above. The IRB is not authorized to extend the approval period for any research project.

19.2 Re-activation of Terminated Protocols

A protocol that has been terminated, for any reason, cannot be re-activated unless it is re-reviewed and approved by the IRB. If a PI wants to re-activate a terminated protocol, he/she must submit a progress report within 90 days of the study expiration date. If a progress report – continuation review is not submitted within 90 days of the expiration date, the PI must re-submit it to the IRB in accordance with the requirements for new protocols.

In addition to the protocol application, the PI may be required to submit a Report of Major Protocol Violation to the IRB, detailing the circumstances which led to the protocol closure, along with his/her reasons for re-activating the protocol. If termination was due to administrative problems (e.g., a delinquent progress report), he/she must include a description of the corrective action he/she has taken in order to avoid such closures in the future.

19.3 Modifications

Changes (amendments/modifications) to a protocol may not be initiated without prior IRB approval, except when necessary to eliminate immediate hazards to the subjects. When changes are implemented to eliminate an immediate hazard, the IRB must be notified of the change promptly (within 3-5 business days).

19.3.1 Major modifications are changes to the protocol that alter the risk/benefit ratio for study subjects, that significantly change or affect the conduct of the study, and include any new information that may affect safety and/or willingness of subjects to participate.

19.3.2 Minor modifications are changes that do not alter the overall risk-benefit profile of the study, would not potentially affect the willingness of enrolled subjects to remain in the study, or the willingness of potential subjects to enroll in the study, and do not alter the scientific validity of the study design.

It is the responsibility of the PI to submit, in a timely manner, all protocol modifications, revised consent forms, changes in investigators, changes to FDA Form 1572 (for clinical trials), and any other information which may affect the conduct of the research study.

Minor changes in the protocol and/or consent form, may be reviewed through the expedited review procedure (see Expedited Review). However, all other changes will be reviewed by the IRB at a convened meeting, in which case deadline dates for submission apply.

19.3.3 How to Submit Modifications to the IRB: A request for a change in key personnel or other study modifications are summarized and reported in *Iris*

19.4 Protocol Exceptions

A protocol exception is any temporary protocol deviation that is approved by the IRB prior to its initiation, e.g., enrollment of a subject who does not meet the eligibility criteria. The PI should only request approval for exceptions that could affect a subject's safety, welfare, comfort or rights.

19.4.1 How to Request a Protocol Exception In order to obtain approval for a protocol exception, the PI must submit a request though *Iris.*

All approved protocol exceptions should be listed on the progress report.

19.4.2 IRB Response/Action The Office of Research/IRB will process protocol exception requests. Each request will be evaluated on a case-by-case basis by the IRB Chair or designee, and when appropriate, by the convened IRB committee. Investigators will be informed in writing regarding the IRB's decision. No exception may be implemented without IRB approval.

19.5 Protocol Violations

A protocol violation is a deviation that is not approved by the IRB prior to its initiation or implementation. Protocol violations may be major or minor:

A **major protocol violation**:

1. Affects subject safety
2. Damages the scientific integrity of the data collected

3. Affects a subject's willingness to participate in the study

Examples of **major protocol violations** include (but are not limited to):

1. Failure to obtain informed consent (i.e., no documentation of informed consent, consent obtained after study procedures were initiated)
2. Informed consent for IND/IDE studies obtained by unauthorized individuals (i.e., someone other than a licensed physician investigator)
3. Enrolling a subject who does not meet inclusion/exclusion criteria
4. Use of study procedures not approved by the IRB
5. Failure to report a serious adverse event to the IRB and/or sponsor
6. Failure to perform a required lab test that could affect subject safety or integrity of data
7. Error in dispensing or dosing of drug/study medication
8. Error involving use of a device
9. Study visit conducted outside of required timeframe, only if it affects subject safety
10. Failures to follow safety monitoring plan
11. Failure to submit a continuing review application to the IRB before study expiration
12. Missing subject signature on consent form
13. Missing investigator/person consenting signature on consent form
14. Use of invalid consent form (i.e., use of outdated or unapproved consent form)
15. Enrollment of subjects after IRB-approval of study expired

A **minor protocol violation**:

1. Does not affect subject safety
2. Has no effect on value of the data collected
3. Does not affect a subject's willingness to be in a study

Examples of minor protocol violations include (but are not limited to):

1. Missing original signed and dated consent form (only photocopy available)
2. Inappropriate documentation of informed consent, including:

    - Copy not given to the person signing the consent form
    - Someone other than the subject dated the consent form

3. Deviations from the approved study procedure that do not affect subject safety or data integrity

    - Study procedure conducted out of sequence
    - Omitting an approved portion of the protocol
    - Failure to perform a required lab test
    - Missing lab results
    - Study visit conducted outside of required timeframe

4. Failure of subject to return study medication

It is the responsibility of the PI to determine if a violation is major or minor. Major protocol violations must be reported to the IRB within ten (10) working days of discovery. Minor protocol violations may be reported at continuing review. Reports of protocol violations should be submitted to the sponsor according to the sponsor's protocol.

19.5.1 How to Report a Protocol Violation to the IRB - Major protocol violations should be submitted to the Office of Research/IRB through *Iris.*

19.5.2 Correcting Protocol Violations - The PI is responsible for ensuring that a systematic review of protocol violations is conducted. The review should determine the root cause of the problem and address the underlying issue to prevent a recurrence. The root cause analysis includes the following steps:

1. Define the problem/gather the facts
2. Assemble an interdisciplinary team
3. Determine the sequence of events
4. Identify contributing factors
5. Select root causes
6. Develop corrective action & follow-up plan

19.5.3 IRB Response/Action Reports of major protocol violations are reviewed by the IRB chair or designee, Administrative Liaison/IRB and/or Regulatory Readiness Coordinator. Further inquiry or review may be initiated depending on the violation. If the violation proves to be serious, the IRB chair or designee may choose to suspend or terminate the protocol. The report and any action taken by the IRB chair or designee, Administrative Liaison/IRB and/or Regulatory Readiness Coordinator on behalf of the IRB will be reported at the next convened meeting.

If review indicates that the violation is a result of non-compliance, the matter may be referred to the full IRB for further consideration. Actions taken to suspend or terminate a study due to a major protocol violation will be reported to the Institutional Official, the department head (as appropriate), the FDA (as appropriate), any funding agency (as appropriate), and the OHRP (as appropriate). Any subsequent action, such as changing or lifting a suspension will also be reported to the appropriate agencies and/or department heads. Reports may also be shared with other IRBs having responsibility for the study. Investigators will be informed in writing of all IRB inquiries and determinations.

19.6 Serious Adverse Events / Adverse Events/Unanticipated Problems

It is the responsibility of the PI to promptly report any serious problems involving risks to subjects or others to the IRB. This reporting is in addition to, and does not supplant, periodic progress reports.

9.6.1 How to Report an Adverse Event to the IRB All reportable events should be reported in *Iris*:

Go to the tab, "Submissions" and then "Internal External Serious Adverse Event. (Instructions are available in the "Operating Procedures" section of *Iris)*

Report should include:

1. A detailed description of the event
2. Category of event - expected or unexpected
3. Any resultant changes to the consent form
4. Event relation to study intervention
5. Rationale for assessment
6. Outcome
7. Site of incident

For internal reportable events, the PI must attach supporting information and materials such as progress notes, lab findings, death certificates, etc.

To report **serious external adverse events, t**he investigator's report should include:

1. A detailed description of the event
2. Any resultant changes to the consent form
3. TMH investigator's assessment of event
4. Site of incident

For external reportable events, the PI must attach supporting information and materials such as letters from sponsor, Medwatch reports, site investigator reports, progress notes, etc.

Iris should be used to report unanticipated problems involving risks to subjects or others. The investigator's report should include:

1. A detailed description of the event
2. Effect on subjects
3. Effect of study validity
4. Corrective action

The PI is the sponsor of investigator-initiated studies. As such, he/she must follow mandatory FDA reporting requirements. (See www.fda.gov/medwatch/how.htm). Copies of any reports submitted to the FDA should be sent to the IRB.

19.6.2 IRB Response/Action - All reported serious adverse events receive review by the IRB chair/designee, IRB/Administrative Liaison or Office of Research/IRB staff.

All such events will be acknowledged by the IRB according to their severity and relation to the study.

The IRB or IRB chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the PI. The IRB or IRB chair/designee shall promptly report its findings to the investigator and, if warranted, to Institutional Officials, study sponsor, Office of Human Research Protection (OHRP), and the FDA.

19.6.3 Reporting Requirements for External Adverse Events - The FDA requires sponsors to notify all participating investigators of any serious and unexpected adverse event associated with the use of a test article that occurs at one of the participating sites of a multi-center study. These reports must be submitted to the IRB by the investigator as they are received, i.e., one week of the investigator becoming aware of the event, **if** the events are deemed related to the study agent. An assessment must be made by the principal investigator to determine whether or not a change to the consent form or other study documents are necessary as a result of the information in the report. If reports are received by an investigator in the form of a series of safety reports, or a periodic Data Safety Monitoring Board (DSMB) Report (often a compilation of adverse events), and meets the reporting requirements outlined above (i.e., serious, unexpected and related events) the investigator shall provide a written summary to the IRB along with the report.

When sponsor submission requirements and IRB policy are discordant, the IRB guideline shall be followed.

The following types of external serious adverse event reports should NOT be sent to the Office of the Research / IRB:

- Expected events
- Unrelated events

If the Office of Research/IRB receives any reports that fit these two criteria, they will be sent back to the PI without acknowledgement.

19.6.4 IRB Response/Action - All reported serious adverse events receive review by the IRB chair/designee, IRB/Administrative Liaison or IRB staff.

All such events will be acknowledged by the IRB according to their severity and relation to the study

The IRB or IRB chair/designee has the authority to suspend, and the IRB has the authority to terminate, approval of research at its site that has been associated with unexpected serious harm to participants. When the IRB or IRB chair/designee takes such action, a statement of reasons for such action shall be included in a notification letter to the PI. The IRB or IRB chair/designee shall promptly report its findings to the investigator and, if warranted, to Institutional Officials, study sponsor, Office of Human Research Protection (OHRP), and the FDA.

19.7 Withdrawal of a Protocol

If a PI decides not to implement an IRB approved study, the IRB must be notified, preferably in writing, requesting study withdrawal.

Section 20

Emergency Use of a Test Article – Early / Expanded Access

20.1 Emergency Use Exemption of a Test Article

FDA defines emergency use (vs emergency research) as the use of an investigational drug or biological product in a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. The emergency use provision in the FDA regulations [21 CFR 56.104 (c)] is an exemption from prior review and approval by the IRB of a *single* patient use of a drug, device, or biologic considered to be investigational; however, reporting the use to the IRB is required by the FDA. Under DHHS regulations, patients receiving a test article in emergency use may not be considered research participants.

Specific access programs such as an **Open Label Protocol** or **Treatment IND** for a **single subject** or **group of subjects** are available for the use of test articles outside of formal clinical trials. These studies require prospective IRB review and informed consent.

20.2 Criteria for Emergency Use Exemption

The emergency use exemption of an investigational drug, biologic or device requires that all of the following conditions be met:

1. The test article is used one time per institution to treat a single patient;
2. The patient has a life threatening condition necessitating use of test article (Note that having an ultimately fatal condition does not constitute a life-threatening emergency);
3. No standard acceptable treatment is available; and
4. There is not sufficient time to obtain full IRB approval.

20.3 Physician Responsibilities for Emergency Use

When time permits, the physician will be asked to complete and submit, in advance, the "Emergency Use of a Test Article" which includes:

1. A brief summary of the clinical history of the subject;
2. The proposed therapy and rationale for therapy;
3. Documentation of authorization from the holder of the IDE/ IND, if one is available;
4. Documentation of FDA notification;
5. A copy of the informed consent document signed by the patient or legally authorized representative;
6. Authorization from the sponsor and FDA IND or IDE information, if available;
7. Independent assessment by a physician who is not participating in the investigation;

8. A written description of the circumstances that warrant the administration of a test article without IRB approval including confirmation that no alternative method of approved or generally recognized therapy is available to provide an equal or greater likelihood of saving the subject's life.

If there is no time to find an uninvolved physician, the clinical investigator makes the determination and documents that there is:

1. a life threatening disease / condition;
2. an immediate need;
3. no alternative;
4. an assessment of potential benefit and substantial reason to believe benefit will occur

Immediately following the start of business hours, the physician must notify the IRB that the test article was initiated. The physician must then submit the required documents identified in the " to the Office of Research / IRB within five working days.

20.4 IRB Responsibilities Related to Emergency Use Exemption Review for Drugs and Devices

The IRB responsibilities include:

1. Reviewing the request by the IRB Chair, the Vice-Chair or designated person to ensure that the requirements of 21 CFR 56.104 (c) are met.
2. Generating a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104 (c) necessary to facilitate the release of the test article from the manufacturer. This statement is not an "IRB approval."
3. Approving request at a full Board. Concurrence of exemption from full IRB review will be acknowledged for one patient only.
4. Reviewing subsequent requests for the same therapy. These requests must be submitted as a research or treatment protocol to the full IRB at a convened meeting.

The FDA does acknowledge that if a second patient were to require the same therapy, it would be inappropriate to deny clinically appropriate emergency treatment to the second individual if the only obstacle is a lack of sufficient time for the IRB to convene a meeting to review the issue.

20.5 After Business Hours Emergency Use Exemption Review for Drugs and Devices

If an event that qualifies for an Emergency Use Exemption occurs on a weekend, in the evening, or time is so short that it is not possible to submit the required materials prior to using the test article or procedure, the investigator may proceed to administer and/or treat the subject.

Immediately following the start of business hours, the investigator must notify the Office of Research/IRB by phone, email, or in writing that the test article or therapy was initiated. The investigator then has **five (5) working days** to submit to the Office of Research/IRB the required written materials which provide the retrospective documentation to determine that the criteria for an Emergency Use Exemption were met. This will be reviewed with the IRB Chairperson. The Report of Emergency Use of a Test Article without IRB Review IRB form 10a acknowledging this retrospective review will be provided to the clinician/investigator.

20.6 Obtaining an Emergency Investigational New Drug (IND-tracking number) for Drugs and Biologics

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, standard procedure is to contact the manufacturer to 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 cases, 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 means of communication.

Section 21

Compassionate Use – Early / Expanded Access

The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group.

21.1 Criteria for Compassionate Use

1. Serious disease or condition
2. No alternative
3. Patient does not meet inclusion criteria for clinical investigation

21.2 Sponsor Responsibilities for Compassionate Use

Prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a compassionate use under section §812.35(a) in order to treat the patient. The IDE supplement should include:

1. A description of the patient's condition and the circumstances necessitating treatment

2. A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
4. The patient protection measures that will be followed. (Informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor)

In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

21.3 Physician Responsibilities related to Compassionate Use

The physician should not treat the patient until FDA approves the use of the device under the proposed circumstances.

If the request is approved, the attending physician is responsible for:

1. Consenting the patient / representative;
2. Devising an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient;
3. Detecting possible problems;
4. Obtaining an independent assessment from an uninvolved physician;
5. Obtaining institutional clearance from the IRB;
6. Reporting any problems as a result of the device to the IRB;
7. Writing a summary of the use and give to the sponsor;
8. Completing a follow-up report to FDA as an IDE Report in which summary information regarding patient outcome is presented.

21.4 IRB Responsibilities related to Compassionate Use:

The IRB is responsible for:

1. Documenting the IRB Chair’s approval;
2. Ensuring FDA concurrence;
3. Reviewing the consent document;
4. Receiving reports of problems;
5. Receiving reports after use.

21.5 Compassionate Use for a Small Group

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from a serious disease or condition for which no alternative therapy adequately meets their medical need. In this case, the physician should request access to the investigational

device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE Report after all compassionate use patients have been treated.

Section 22

Treatment Use – Early / Expanded Access

22.1 Treatment Use of Investigational New Drug (IND) or Investigational Device Exemption (IDE)

The purpose of the Treatment IND exemption is to facilitate the availability of promising test articles to seriously ill patients, as early in the development process as possible, and to obtain additional data on the test article's safety and effectiveness. The Treatment IND protocol is added to an existing investigational new drug application (IND), and allows the use of a test article in a group of subjects who are not enrolled in a clinical study testing the safety and efficacy of the test article.

- For use in seriously ill patients, there must be sufficient evidence that the test article is probably safe and effective; usually, such evidence becomes available during Phase 3 investigations or after all clinical trials have been completed;
- For use in patients, whose life is in immediate danger, information available must be sufficient to conclude that the test article may be effective for the intended use, and would not expose the patient to an unreasonable risk; usually, this information becomes available early in Phase 3, or sometimes in Phase 2 of clinical trials;
- There is no satisfactory alternative treatment available;
- The drug or device sponsor is actively pursuing marketing approval.

The physician intending to initiate a Treatment IND protocol shall be the investigator of a study involving the test article, which has been reviewed and approved previously by the IRB. The investigator shall have received permission of the holder of the IND exemption (sponsor of the research) to use the test article for treatment purposes. The physician shall submit an application to the IRB prior to the initiation of the protocol, following the procedures described in the section for initial review. Procedures for continuation review will be applicable to Treatment IND protocols. The accompanying informed consent document shall be particularly explicit in regards to the use of a test article in a health care setting and the assessment of the risk/benefit relationships.

Section 23

Humanitarian Use Devices

A humanitarian use device (HUD) is a device that can be used to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals per year in the United States. FDA regulations related to the clinical use of an HUD are described in 21 CFR56 (21 CFR 814.124).

A humanitarian use device may also be used in an investigational study; this occurs when the physician or health care provider intends to collect data from the HUD's use. Such investigational use is subject to the same requirements that apply to all FDA-regulated clinical studies and requires a full study application.

Documentation of the Use of a HUD is done in Section 4 of *Iris*, under "Application Selection."

22.1 Physician Responsibilities for the Clinical Use of a HUD

The physician must include in the IRB application the following information about the proposed **clinical** use of the HUD:

1. The FDA HDE (Humanitarian Use Device Exemption) number and approval order;
2. A description of the device;
3. The product labeling;
4. The patient information brochure, if available;
5. The informed consent form , if available (but not required);
6. The proposed use of the device, including a description of any screening procedures, the HUD procedure and any patient follow up visits, tests or procedures;
7. Documentation of the qualifications and training of the health care providers who will use the HUD.

23.2 IRB Submission Requirements for Use of a HUD

When the device is used for clinical purposes, the physician must submit an application that includes all the above information for IRB review at a convened meeting.

When the device is used in an investigational study, an IRB review of the protocol, informed consent and HIPAA authorization is required; and all related IRB guidelines apply.

23.3 Continuing Review Requirements

The physician is responsible for fulfilling continuing review requirements to the IRB at least annually; this may be done through the expedited review process when the device

is used for clinical purposes. The following information must be provided to the IRB when the clinical device is used:

1. Consideration of the risk and benefit information, if available;
2. Copies of safety information in the periodic reports required by the FDA

When the device is used in research, the usual renewal process applies.

23.4 Adverse Events and Unanticipated Problems

Adverse events and unanticipated problems that results from the use of a humanitarian device are subject to the IRB unanticipated problem reporting requirements.

The physician or health care provider is required to promptly report any FDA action(s) regarding the HUD to the IRB.

23.5 Modifications to the HUD

Modifications to the use of HUD or the clinical investigation of the HUD are to be promptly reported to the IRB in accordance with the IRB policy for modifications.

23.6 Emergency Use of a HUD

Off-label use of a HUD in an emergency situation that cannot wait for IRB review may be used without prior IRB approval. Before using the HUD, the physician should take as many of the following patient protection measures as possible:

- Contact the IRB Chair and obtain concurrence for the use of the HUD, if there is time;
- Obtain treatment informed consent from the patient or his/ her legally authorized representative;
- Provide the patient with the HUD patient information packet, if available, before or immediately following the use of the device;
- Develop a monitoring schedule, taking into consideration the patient's specific and the limited information available about the risks and benefits of the device

The physician must, within five days after the emergency use of the device, provide written notification of the use to the IRB Chairperson. This documentation must include identification of the patient, the date of use, the reason for use and proposed monitoring. In addition, there is FDA reporting to the holder of the HDE.

Section 24

Human Biologic Materials

24.1 Genetic Analysis on Biological Specimens Obtained In Human Subject Research

Research using anonymous samples (without linkage) is eligible for exemption from IRB review [45 CFR 46.101(b)(4)]. Research conducted with coded or identified samples is considered research on human subjects and requires full IRB review. When informed consent to the research use of human biological materials is required, it should be obtained separately from informed consent of clinical procedures.

24.2 Categories of Human Biological Materials

Categories of human biological materials include:

1. Unidentified or anonymous samples: supplied by repositories without identifiers;
2. Unlinked or anonymized samples: lacking identifiers or codes that can link a sample to a particular human being;
3. Coded sample: samples are coded in such a way that they could be traced to a particular individual;
4. Identified samples: a personal identifier, such as a name, hospital number, or social security number allows the researcher to link the sample directly to a particular individual.

24.3 Creating Unlinked Samples

When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, the IRB may exempt the research from informed consent if it determines that the process used to unlink the samples will be effective, and the unlinking of the samples will not reduce the value of the research.

423.4 Research with Repository Collections

Research with existing specimens (repository collections) may include specimens if there are no identifiers and the samples are not coded. If an existing biological specimen has been obtained from a patient or a human subject without explicit consent for genetic analysis, the specimen must be stripped of any identifiers which could link the specimen to the person from whom the sample was obtained.

24.5 Identified Specimens

If the investigator wishes to retain identifiers, even if the samples are coded, explicit consent for genetic analysis must be obtained from the subject.

24.6 Research Using Human Biological Materials

A biological specimen, which is identifiable or which is coded but linked to the subject, may be submitted for genetic analysis only if a separate informed consent document is executed, which includes the following information:

1. The specific purpose of the genetic analysis;
2. The particular genetic information to be acquired;
3. The potential consequences of the genetic information to future insurability, employability, or social welfare of the subject;
4. Whether or not the genetic information will be linkable to the subject;
5. Whether or not the genetic information will be given to the subject;
6. Any provision for genetic counseling if genetic information will be given to the
7. subject;
8. The likelihood of commercialization of the new knowledge that could result in
9. potential financial gains;
10. The likelihood that the tissue samples or genetic material derived from those samples will be shared with other researchers;
11. Consent for genetic tissue samples can be obtained only from a competent subject if a coded identified sample is used.

24.7 Human Biological Materials Protocol Document Requirements

When reviewing and approving a protocol for research on human biological materials, this IRB will require the investigator to set forth:

1. A thorough justification of the research design, including procedures used to minimize risks to subjects;
2. A full description of the process by which samples will be obtained;
3. Any plans to obtain access to the medical records of the subjects;
4. A full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information; and
5. An informed consent document which indicates whether individuals want their sample to be used in future research and in some instances may specify the type of research.

24.8 Human Biological Materials Informed Consent Document Requirements

Informed consent documents should be developed to provide potential subjects with a sufficient number of options to help them understand clearly the nature of the decision they are about to make. Such options might include:

1. Refusing use of their biological materials in research;
2. Permitting only unidentified or unlinked use of their biological materials in research;
3. Permitting coded or identified used of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies;
4. Permitting coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies; or
5. Permitting coded use of their biological materials for any kind of future study.

Section 25

Research versus Quality Improvement

25.1 Research

Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge**.** All research requires the patient's consent, unless formally waived and the approval by the IRB.

25.2 Quality Improvement

Quality improvement (QI) is an assessment by the organization of patient care including safety / quality, access, service and cost for the purpose of improvement through peer analysis, intervention, and resolution of the problem and follow up.

Characteristics of QI include:

1. QI is designed to bring immediate, continuous improvements in healthcare delivery
2. QI is designed to have its findings applicable to the local institution although it may also benefit other organizations, working on the same issue
3. QI is designed to sustain improvements
4. QI does not require fixed, rigid protocols; it is acceptable to adapt the project over time.

To determine if a quality improvement activity requires IRB approval, the following questions should be addressed:

1. Does the activity involve research (45 CFR 46.102(d))
2. Does the activity involve *human subjects* (45CFR 46.102(f))
3. Does the human subject activity qualify for an exemption (45 CFR 46.101(b))
4. Is the nonexempt human subject activity conducted or supported by HHS or otherwise covered by the FWA approved OHRP

Data from QI projects cannot be shared outside the organization. If there is a desire to publish the findings of the QI project, there needs to be the approval of the Research Council.

The IRB cannot issue retroactive approval of an activity that is conducted as a QI project and is later determined to be human research.

25.2 Difference between Quality Improvement and Research

The key difference between quality improvement and research is that research studies are intended to create new knowledge that can be generalizeable to other populations and settings, while QI in health care uses existing knowledge to improve health care outcomes within a local health care institution or setting.

	Research	**Quality Improvement**
Purpose	Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge**.** All research requires the patient's consent, unless formally waived and the approval by the IRB	Quality improvement (QI) is an assessment by the organization of a patient care problem for the purpose of improving patient care through peer analysis, intervention, and resolution of the problem and follow up.
Starting Point	To answer a question or test a hypothesis with the intention of contributing to generalizable knowledge	To answer a question or test a hypothesis with the intention of measuring or improving performance.
Design / Methods	Follows a research design (i.e. control groups, random selection of subjects, statistical analysis) that will lead to scientifically valid findings.	Uses established quality improvement methods (i.e. IHI model for improvement, PDSA cycles) aimed at producing a change within the hospital.
Risks / Burdens	May put participants at risk (including privacy risk) and added burden.	Does not increase risks to participants.
Benefits	Knowledge sought may not benefit current participants.	Knowledge sought may directly benefit process / program service at TMH; and may or may not benefit patients.
Data Collection	Involves systematic data collection.	Involves systematic data collection.
Testing Analysis	Statistically proves / disproves hypothesis.	Uses details of qualitative and quantitative methods to draw inferences from data.
End Point	Answers a research question and or invites critical appraisal of the conclusion by peers through presentation	Improve a program, process or service; implements, monitors and sustains improvement

[1] National Health and Medical Research Council, *When does quality assurance in health care require independent ethical review?* Endorsed 20 February 2003 Australia

Section 26
Audits / Quality Improvement

26.1 Routine Audits

The Office of Research/IRB will conduct routine audits of IRB approved studies. The IRB, in conjunction with the Office of Research/IRB, will select the studies to be audited. The goals of the routine audits are to:

1. assure protection of human subjects and data integrity,
2. provide education and training to research staff,
3. ensure that federal, state, and institutional regulatory standards are met.

The Regulatory Readiness Coordinator or designee will notify the PI of the audit in writing and the Office of Research/IRB staff will arrange a time to review the investigator's study files. The audit process will usually include an inspection of the IRB files for the study and an on-site review of the investigator's files and records including:

1. study personnel CVs and licenses,
2. source documents and case report forms,
3. review of information about recruitment and the consent process,
4. informed consent forms (blank and signed versions),
5. subject files and data,
6. subject inpatient or outpatient medical records as appropriate,
7. drug or device accountability records,
8. study samples and shipping receipts,
9. laboratory licenses and certifications,
10. any other documents deemed appropriate.

The Office of Research/IRB will generate a report summarizing the audit findings and recommendations. The Office of Research/IRB will send a draft version of the audit report to the PI for review and will provide the PI with adequate opportunity to respond. A final version will be disseminated to the PI, the IRB, the Office of Research/IRB and appropriate health system leadership. Any routine audit found to have significant issues will be presented to the IRB, which will determine if any action is required (i.e., enrollment hold, etc.). The PI will be required to develop a corrective and preventive action plan, which may require follow-up by the IRB or Office of Research/IRB.

Note: Significant findings may also be reported to external authorities as required (e.g., OHRP, FDA, etc.).

26.2 For-Cause Compliance Audits

When necessary, the IRB may request information beyond regular progress reports in order to ensure the rights and welfare of research subjects are protected. Upon discovery of a potential problem, the IRB or IRB Chair/designee will consider the issues and has the authority to suspend a protocol if a deficiency or situation poses a risk to subjects.

The IRB will notify the Office of Research/IRB in writing with a summary of the issues and ask that a “for-cause” audit be conducted. The Office of Research/IRB will notify the PI in writing that an audit has been requested. The letter will outline the reason for the request and detail any information that is needed. The PI will be given adequate opportunity to respond. The Office of Research/IRB staff or designee will arrange a time to review the investigator’s study files and any other information necessary for the conduct of the audit. The IRB shall be kept apprised of any such action at their monthly meeting. If the Office of Research/IRB audit indicates monitoring is necessary to investigate an immediate concern regarding the safety of study subjects, the IRB Chair/designee may act accordingly without convening an IRB meeting; however, no protocol may be permanently terminated without the concurrence of the full Board at a convened meeting.

Under Department of Health and Human Services regulations, a for-cause suspension of IRB approval must be reported to Office of Human Research Protections (OHRP). Any suspension resulting from a for-cause audit will be immediately reported to the Institutional Official, department chair, funding agency (if applicable), OHRP, and, if a drug or device is involved, the FDA. Other IRBs that are relied upon by the IRB at TMH may also be notified regarding findings regarding investigator compliance as appropriate.

For-cause audits may also be prompted by information obtained from sources outside the IRB, such as internal/external whistleblowers, regulatory agencies, industry sponsors, or research subjects. Information from any of these sources that raise concerns about a protocol will be directed to the Office of Research/IRB.

26.3 Monitoring Research Accounting Practices

The IRB relies on the Tallahassee Memorial HealthCare Compliance Program to monitor research accounting practices for:

1. Inappropriate billing;
2. Improper use of grant monies received by TMH or its employees / affiliates;
3. Compensation to TMH from sponsors in amounts greater than fair market value for services provided.

Section 27

IRB Records

27.1 Protocol Archives

The IRB will maintain records for all research projects approved by the IRB. Documentation for each study will include the following types of documents:

1. Application forms;
2. Consent documents, all versions submitted;

3. Research protocol;
4. Investigator's brochure for test articles;
5. Certification documents from other agencies, as mandated by federal regulatory agencies;
6. Texts of advertisements for subject recruitment;
7. Notifications of IRB decisions;
8. Records of continuation review activities;
9. Reports on amendments and adverse events;
10. Statements on significant new findings;
11. Correspondence between IRB and investigators of the project;
12. Copies of the informed consent documents signed by subjects. Subject names are redacted to protect confidentiality unless there is a documented reason to maintain the name.

27.2 IRB Record Retention

Active IRB records are considered confidential and are maintained in a secured manner. Only Office of Research/IRB Staff, Board members or authorized individuals, i.e., regulatory agencies, may have access to the records. The records may not be released to the PI. The Office of Research/IRB Staff will assist the PI as necessary when information from the records is needed.

The records of an approved research project are retained for three years after completion of the research. During this time, the records shall be maintained in a manner as to be accessible at reasonable times and in a reasonable manner for inspection by regulatory agencies, as permitted by law. Withdrawn studies files are retained for three years from the time the study number is issued. After three years, unless otherwise requested by the study sponsor, paper files are shredded

27.3 IRB Membership Records

An IRB membership roster is maintained. The IRB roster identifies members by name, degrees, affiliations, and representation capacity. Curricula vitae/resume of active members of the IRB is maintained in the records of the IRB, and updated in content upon reappointment. Each member's membership term status is monitored and updated.

Documentation of orientation to the IRB and basic education is maintained in the IRB membership records.

Section 28

Reference Materials

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