Policies and Operations Manual

for the

Institutional Review Board

of

Tufts Medical Center

and

Tufts University Health Sciences
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1 Abbreviations Used in this Manual

The following abbreviations are used throughout this manual:

- AHRQ: Agency for Healthcare Research and Quality
- CDC: Centers for Disease Control and Prevention
- CFR: Code of Federal Regulations
- CEO: Chief Executive Officer
- CIRB: Central Institutional Review Board (refers to NCI CIRB)
- Co-I: Co-Investigator
- COI: Conflict of Interest
- Common Rule: Principals of 45 CFR 46 Subpart A
- CR: Continuing Review
- DHHS: Department of Health and Human Services
- DoD: Department of Defense
- DoE: Department of Energy
- DoJ: Department of Justice
- DSMB: Data and Safety Monitoring Board
- EPA: Environmental Protection Agency
- FDA: U.S. Food and Drug Administration
- FD&C Act: Federal Food Drug and Cosmetic Act
- FWA: Federalwide Assurance of Compliance
- GCRC: General Clinical Research Center
- HIPAA: Health Insurance Portability and Accountability Act of 1996
- IB: Investigator’s Brochure
- ICF: Informed Consent Form
- IDE: Investigational Device Exemption
- IND: Investigational New Drug
- IRB: Institutional Review Board
- IRB EC: IRB Executive Committee
- JCAHO: Joint Committee on Accreditation of Healthcare Organizations
- MA DPH: Massachusetts Department of Public Health
- MGL: Massachusetts General Laws
- MPA: Multiple Project Assurance

1 The “Common Rule” refers to 45 CFR Part 46, Subpart A, the basic principals that apply to human subject protections, which were adopted in 1991 by most federal agencies in response to the convergent DHHS and FDA regulations. Officially, Subpart A defines the Common Rule. The remaining Subparts B, C & D were added subsequently and are not officially recognized as part of the Common Rule. However, when the Common Rule is referred to it is generally considered to include Subparts B, C & D.
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MSDS: Material Safety Data Sheet
NCI: National Cancer Institute
NIH: National Institutes of Health
NSR: Non-Significant Risk
OHRP: Office for Human Research Protections2
PI: Principal Investigator
RSO: Radiation Safety Officer
SAE: Serious Adverse Event
SPA: Single Project Assurance
SR: Significant Risk
SRC: Scientific Review Committee
Tufts MC: Tufts Medical Center
TUHS: Tufts University Health Sciences
UA: Unanticipated Event
UP: Unanticipated Problem
WIRB: Western Institutional Review Board

2 Formerly the Office for Protection from Research Risks (OPRR).
2 Introduction

2.0 Purpose

The purposes of this operations manual are:

- To provide the basic operational guidelines, polices, and procedures of the Tufts Medical Center (Tufts MC) and Tufts University Health Sciences (TUHS) Institutional Review Board (IRB) in accordance with 45 CFR 46;

- To delineate the responsibilities of the Institutional Officials for the Tufts MC and TUHS, the Executive Committee, the IRB\(^3\), and the IRB office\(^4\);

- To consolidated IRB guidelines, policies, and procedures hitherto contained in a variety of documents, the FWA, and various other documents relied upon by the IRB.

An IRB is a federally mandated entity charged with ensuring the ethical principles governing research involving human research subjects, regardless of the funding source.\(^5\) The policies and procedures governing the IRB include, but are not limited to, those that are detailed in this manual.

For the purposes of this manual, research is defined per 45 CFR 46: a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research, whether or not they are conducted or supported under a program which is considered research for other purposes.

Any person wishing to suggest a new or revised policy, procedure or form is invited to submit the suggestion in writing to the Manager of IRB Operations, along with a description of the rationale for the change.

\(^3\) The Tufts MC and TUHS Institutional Review Board utilizes a system comprised of the IRB-RED and IRB-BLUE committees. These committees will be referenced as a single entity (“IRB”) throughout this document.

\(^4\) When, for clarity of understanding, it is necessary to distinguish between the IRB committees and the administrative office, the term “IRB office” is used.

\(^5\) The HHS regulations (45 CFR part 46) apply to research involving human subjects conducted by the HHS or funded in whole or in part by the HHS. The FDA regulations [21 CFR parts 50 and 56] apply to research involving products regulated by the FDA. Federal support is not necessary for the FDA regulations to be applicable. The vast majority of institutions/entities, including Tufts MC and TUHS, (e.g. Federalwide Assurance [formerly Multiple or Single Projects Assurance] apply HHS regulatory requirements to all research conducted under their auspices. Thus, typically, industry-sponsored, privately funded research, etc., are subject to the same requirements as federally funded research.
3 Organization

This section provides an overview of the structure, responsibilities, and membership of the IRB.

- The Institutional Review Board
- Membership of the IRB
- Scientific Review Committee (SRC)

3.0 The IRB

The IRB functions under FWA 00004449 with respect to Tufts MC and under FWA 00004517 with respect to TUHS, both of which are granted by the DHHS. The IRBs operate under IORG0000435 (IRB # 0000577 #1 (Red), IRB # 0001236 #2 (Blue)), per OHRP. The IORG number is a unique number assigned by OHRP to the institution the first time the institution registered an IRB. Per 45 CFR 46.501, the IRBs are registered as OHRP/FDA entities.

The IRB is responsible for reviewing research involving human subjects at these institutions, and their affiliates, to ensure that subjects’ safety, rights, and welfare are protected in conformity with applicable regulations and guidance issued by the DHHS and the FDA, and other federal agencies, as applicable.

The IRB is also responsible for ensuring conformity with applicable Massachusetts state and local laws and regulations where such laws or regulations provide protection for human subjects that exceed the protection afforded under federal law. In addition, guidelines and requirements imposed by the Institutions that exceed federal, state or local laws are applicable.

The IRB is organized under the Tufts MC Office of Research Administration and the Tufts University Office of the Vice Provost.

3.0.1 IRB

Two committees, the IRB-RED and the IRB-BLUE, each convene on a monthly basis to review research involving human subjects. Additional meetings may be scheduled, as needed, to accommodate a high volume of research submitted to the IRB. In the event that there is no new research to be presented to a convened IRB and no studies that require continuing review by a convened IRB, the Institutional Officials and the IRB Chair may cancel or reschedule a meeting.

3.0.2 IRB Office

The IRB office will facilitate the IRB’s fulfillment of its review responsibilities. The IRB office is overseen by the Manager of IRB Operations and is staffed by other professional and support personnel.

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6 Tufts MC and TUHS were previously organized under MPAs M-1440 and M-1448, respectively.
3.0.3 Institutional Officials

Tufts MC has designated the individual occupying the position of Vice President, Research Administration, as the Institutional Official who oversees the activities of the IRB under the FWA 00004449. Tufts University has designated the individual occupying the position of Vice Provost for Research as the Institutional Official who oversees the activities of the IRB under FWA 00004517.

3.0.4 Executive Committee

An Executive Committee, comprised of the Institutional Officials, the IRB Chair and Vice-Chairs, the Manager of IRB Operations, and the IRB Coordinators, serves as a forum for discussion of issues relating to the operations of the IRB.

This committee functions as a steering committee to address policy and procedural matters related to the operations of the IRB.

3.0.4.1 Policies of the Executive Committee (version dated 01/19/07, accepted by the Executive Committee 01/23/07)

The IRB Executive Committee functions as a steering committee for the IRB. As such, it will meet on a regular basis to discuss relevant issues.

The Executive Committee reaches decision by consensus, not by vote.

Minutes of Executive Committee meetings will not typically be taken. Under certain circumstances, the Executive Committee may decide, on a case-by-case basis, to record minutes. In such a case, the minutes would be voted on by the Executive Committee. Any minutes would be confidential and available to members of the Executive Committee only.

3.1 Scope of IRB Review Responsibility

The IRB reviews all human subject research conducted at Tufts MC or Tufts University Health Sciences. In addition, the IRB may from time to time review research from the Tufts University undergraduate campus (FWA00002063). Research designed to use human subjects, tissues or materials from living humans, or data about humans must be formally reviewed and approved, or granted an exemption, by the IRB before the research begins, if any of the following are true:

- Institutions become “engaged” in human subject research when its employees or agents intervene or interact with living individuals for research purposes; or, obtain individually identifiable private information for research purposes.\(^7\)

- An institution is automatically considered to be "engaged" in human subject research whenever it receives a direct DHHS award to support such research. In such cases, the awardee institution bears ultimate responsibility for protecting human subjects under the award.

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\(^7\) OPRR policy guidance, *Engagement of Institutions in Research*, issued 16 October 2008
The research is sponsored by the Tufts MC or the TUHS ("the institutions").

- Tufts MC includes all clinical and biomedical services incorporated within the Tufts MC and the Floating Hospital for Children at Tufts MC.

- TUHS includes the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA), the Schools of Medicine, Dental Medicine, Veterinary Medicine, the Sackler School, and the Friedman School of Nutrition.

The research is conducted by, or under the direction of, any health care personnel, employee, or agent of the institutions in connection with his or her institutional responsibilities, or by students under the formal guidance of an academic mentor(s).

An employee, or agent of the institutions, conducts the research at his/her private office in accordance with the mission of the institution.

The research is conducted by, or under the direction of, any health care personnel, employee, agent, student, or affiliated individual or entity requiring access to, or using any property of, the institutions’ facilities.

The research involves the use of any of the institutions’ nonpublic information (e.g. paper or electronic medical records, research databases, address or class lists, etc.) to identify or contact existing or prospective human research subjects.

In some instances, particularly where the data or material were not obtained for research purposes and contains no identifiers (10 August 2004, Guidance on Research Involving Coded Private Information or Biological Specimens) the research is not considered human subjects research, and is not within the scope of the Tufts MC or Tufts University IRB review. In these instances the IRB will make a determination that the research is not human subjects research, and provide a letter to this effect to the investigator. Refer to section 4.1 for additional information pertaining to Not Human Subjects Research.

### 3.2 Membership of the IRB

In conformity with 45 CFR 46.107 and 21 CFR 56.107 an IRB requires at least five members. Membership will represent a diversity of disciplines. The IRB members shall have varying backgrounds to promote the complete and adequate review of research activities conducted by the institutions. The IRB shall be sufficiently qualified through the experience, expertise, and diversity of its members, including considerations of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the safety, rights, and welfare of human research subjects. In addition, the IRB shall have:

- At least one member whose primary concentration is in scientific areas, such as a physician or scientist;
- At least one member whose primary concentration is in a nonscientific area, such as a lawyer, ethicist, member of the clergy, etc.;
- At least one member who is unaffiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
The Institutional Officials, the Manager of IRB Operations, and the Research Subject Advocate shall be recognized as non-voting ex-officio IRB members. When present at a convened IRB meeting, ex-officio members will not count toward the meeting quorum.

IRB membership lists, changes in IRB structure, and changes of Institutional Officials will be updated by the Manager of IRB Operations or designee and submitted to OHRP, as required. Membership will remain unpublished; however, the research community will know the identity of the IRB Chair and the IRB Vice-Chairs. At the request of the Principal Investigator (PI) or a member of a research team, in lieu of a membership roster, a letter attesting to the status of the FWAs and conformity with state law will be provided.

Recognized alternate IRB members may be used. The IRB registrations will identify the member(s) for whom an alternate may substitute. To ensure appropriate review of studies, concerted effort will be made to ensure that the alternate's qualifications are at least comparable to the member for whom s/he is substituting. Also, the IRB Vice-Chairs may serve as alternates for each other, regardless of specialty. The meeting minutes will document when an alternate substitutes for a member. The alternate member will have received all materials distributed prior to the IRB meeting.

The Institutional Officials, in consultation with the IRB Chair and the Manager of IRB Operations, shall make the appointment of new IRB members. The initial term of appointment will be subject to re-appointment and will be for not more than one year. At the conclusion of a term of appointment, a member may be appointed for an additional term, and may serve successive additional terms. The Institutional Officials will also make reappointments. The reappointment term shall be recommended by the IRB Chair. Consideration will be given to stagger membership reappointment.

The Manager of IRB Operations will maintain a file pertaining to each IRB member. Each IRB member file will contain a copy of:

- Member’s letter of appointment or reappointment(s) from the Institutional Officials;
- Member’s resume at the time of appointment and reappointment;
- Other relevant correspondence relating to the member’s IRB service;
- Documentation of the completion of human subject protection education requirement(s) and any other relevant certificates of completion.

The files pertaining to IRB members are confidential and may be accessed by the Institutional Officials, the Chair, the Vice-Chairs, the Manager of IRB Operations, the IRB office staff, and regulatory oversight personnel.

### 3.3 Roles and Responsibilities

This section discusses the roles and responsibilities of:

- Institutional Officials
- Executive Committee
- IRB office
  - Manager of IRB Operations
IRB Operations Manual

- IRB Coordinators
- IRB Office Staff

IRB

- The IRB Chair
- IRB Vice-Chairs
- Members
- Primary Reviewers
- Secondary Reviewers

Ex-Officio Members

3.3.1 Institutional Officials

The President of Tufts University and the Chief Executive Officer of Tufts MC will choose an individual from their respective institution to act as the Institutional Official. Each Institutional Official will be responsible for implementing his/her institution’s FWA that all human subject research will be guided by the ethical principles of the Belmont Report, in accordance with the relevant regulatory requirements of 45 CFR 46 and with the human subject regulations or policies of any other relevant federal, state, or local Department or Agency.

The Institutional Officials appoint the IRB Chair, Vice-Chair(s), and members.

The Institutional Officials are also responsible for providing adequate resources, staff, security, and space to fulfill his/her institution’s commitment to ensure that the IRB office can perform its responsibilities and facilitate the effective and safe functioning of the IRB.

The Institutional Officials will oversee the activities of the IRB through the following procedures:

- Appointments
  - The Institutional Officials will appoint the IRB Chair.
  - The Institutional Officials may appoint one or more Vice-Chairs who will be responsible to the Institutional Officials and IRB Chair and who may assist the IRB Chair in the performance of his/her duties.
  - The Institutional Officials in consultation with the IRB Chair and the Manager of IRB Operations shall make appointment of new IRB members.
  - The Institutional Officials may appoint ex-officio members to the IRB.
  - The Institutional Officials may appoint ex-officio members to the Executive Committee.

- The Institutional Officials shall be members of, and shall attend at least seventy-five percent (75%) of the scheduled meetings of the IRB Executive Committee.

- Each Institutional Official will make efforts to attend at least one (1) convened IRB meeting per year of each committee.
The Institutional Officials shall be recognized as non-voting *ex-officio* members of the IRB.

At their discretion, the Institutional Officials may request the preparation of an IRB annual report at the end of each calendar or fiscal year, with a copy to the CEO and/or President of each Institution.

The Institutional Officials will direct the Manager of IRB Operations.

The Institutional Officials may receive monthly status reports/updates from the Manager of IRB Operations or designee regarding the preparation of meeting minutes and such other information as may be requested to evaluate the functioning of the IRB. The Manager of IRB Operations will meet with the Institutional Officials on an as needed basis to discuss IRB and IRB office operations. The Chair will attend as needed.

The Institutional Officials, in consultation with the IRB Executive Committee, may decide to increase or decrease the number of committees as necessary to ensure the adequate and efficient review of the research submitted to the IRB.

Proposed revisions to the Operations Manual of the IRB are subject to the approval of the Institutional Officials, with recommendations from the Chair and Manager of IRB Operations.

### 3.4 The IRB Executive Committee (EC)

The EC should meet at least monthly to provide a forum for discussion of issues relating to the functioning of the IRB; however, the EC will only meet when there are issues that require discussion. The IRB Chair, in consultation with the Institutional Officials and the Manager of IRB Operations, will determine the meeting schedule. The EC is composed of the Institutional Officials, the IRB Chair, the IRB Vice-Chair(s), the Manager of IRB Operations, and the IRB Coordinators.

The IRB Chair is also the EC Chair. In the event that legal advice is required, internal and external legal advisors will be available as a resource to the EC.

The EC Chair or designee will present information regarding research non-compliance, suspensions, or terminations to the EC in conformity with the research non-compliance policy appended to this manual. Meeting agenda and materials are typically distributed to the members electronically in advance of the meeting.

The EC is responsible for the development and implementation of policies, guidance, and forms for the effective operation of the IRB. The Manager of IRB Operations or designee is responsible for overseeing the design of forms.

The EC functions in an advisory capacity and typically acts by consensus, not by vote. In the event that a consensus or compromise agreement cannot be achieved, the Institutional Officials will make the final determination.

The Manager of IRB Operations may create a summary of the determinations made by the EC for internal reference; however, formal meeting minutes will not be produced. Access to the summary will be limited to the Institutional Officials and the Chair.

At the discretion of the Institutional Officials, the SRC Chair may be appointed as a non-voting *ex-officio* member of the EC.
3.5 The IRB Office

The primary function of the IRB office is to enable the IRB to carry out its review responsibilities. For more information about roles and responsibilities within the IRB office, see the following sections:

- Manager of IRB Operations
- IRB Coordinators
- IRB office staff

3.5.1 Manager of IRB Operations

The Director of IRB Operations oversees and implements activities to maintain and enhance the principles and practice of human subject research at the direction of the Institutional Officials with input from the IRB Chair. These activities will include, but are not be limited to, education, the creation and preservation of requisite policies and procedures as they relate to human subject research, and the development of future initiatives to further this mission. The Manager of IRB Operations also has the responsibility of ensuring that the IRB and the institutions are in compliance with all applicable regulatory requirements relevant to human subjects protections, will oversee the daily function of the IRB office, and will report to the Institutional Officials. The Manager of IRB Operations will have the following responsibilities, as related to the IRB:

- Oversee and supervise IRB activities and staff, including training and allocation of responsibility within the IRB office;
- Develop and implement policies and procedures necessary to maintain or enhance the function of the IRB and institutional human research protections program;
- Be a member of the EC;
- With the IRB Chair, carry out EC determinations;
- Provide ethical and regulatory guidance as a non-voting ex-officio member of the IRB;
- Serve as a regulatory resource for institutional leadership and investigators related to the conduct of human subject research;
- Direct, supervise, and lead research education initiatives for the institutional research community.
- May attend the SRC meetings;
- Report to Institutional Officials
  - Annual Report: At the request of an Institutional Official, may prepare an annual report on the IRB. The annual report\(^8\) may include a summary and statistics of the yearly activity of the IRB office and comment on any prospective expansion of staff and resources.

\(^8\) As of 2003.
o Provide the Institutional Official with a copy of all IRB meeting minutes;

- Interface with inspectors in the event of a federal or internal audit/inspection;
- Provide analyses of, and recommendation regarding, the triage of research non-compliance; facilitate the investigation of potential research non-compliance in consultation with the IRB Chair and oversee the reporting of research non-compliance to the IRBs;
- Fulfill responsibilities outlined in the Research Non-Compliance and Suspension and Termination policies outlined in this manual. Specifically, interface with relevant regulatory authorities (e.g. OHRP, FDA, etc.) in the potential reporting of research non-compliance, involuntary suspensions and terminations, and reportable serious adverse or unanticipated events;
- Review IRB meeting minutes;
- Submit IRB membership lists, changes in IRB structure, and changes of Institutional structure, personnel, etc., to the OHRP/FDA;
- Maintain IRB member files;
- Update OHRP/FDA IRB Registration;
- Oversee the revision of this manual on an as needed basis.

### 3.5.2 IRB Coordinators

A dedicated coordinator will be assigned to each IRB committee. All responsibilities assigned to an IRB Coordinator will be conducted under the supervision of the Manager of IRB Operations. The IRB Coordinators have the following responsibilities:

- Orient and train new IRB members, in consultation with the IRB Chair and the Manager of IRB Operations;
- In consultation with the Manager of IRB Operations and IRB Chair, assign IRB members to act as Primary and Secondary Reviewers.
- As needed, perform the initial screening (i.e., pre-review) of all greater than minimal risk applications for initial IRB review;
- May pre-review PI responses to IRB review comments. Responses to previously outlined stipulations will be forwarded to the IRB Chair, an IRB Vice-Chair, or designee for review and approval;
- Prepare the agenda for IRB meetings. Materials will typically be distributed electronically to all members expected to attend the IRB meeting at least seven (7) calendar days before the meeting. Circumstances may arise whereby materials are forwarded to IRB members less than 7 calendar days prior to the meeting, e.g., addendum to the agenda, revised or additional materials provided by the PI;
- Ensure that notifications to the IRB are appropriately recorded on a monthly basis (e.g., in-office expedited review of submissions). A compendium of the preceding month’s approvals
will be transmitted electronically to IRB members in sufficient time prior to the next IRB meeting;

- Prepare the notification to the PI of IRB actions, typically within two (2) weeks of the IRB meeting. The Coordinator will prepare the notification of the IRB comments regarding initial review and will prepare the notification(s) regarding modification and continuing review.

- Record meeting minutes, including attendance, votes, and recusals;

- Prepare meeting minutes in a timely manner for distribution with the meeting agenda prior to the next scheduled meeting. The Coordinators prepare the meeting minutes pertaining to initial reviews and supervise the preparation of the meeting minutes regarding modification and continuing review. The Manager of IRB Operations may review meeting minutes prior to distribution to the IRB. The IRB Coordinators will distribute the minutes to the IRB members electronically in sufficient time prior to the next IRB meeting;

- Process research non-compliance;

- Facilitate the review, follow-up, and approval of expedited reviews;

- Serve as a regulatory resource for researchers and co-workers;

- Assist with the training of new staff;

- Assist with the general operations of the IRB office at the direction of the Manager of IRB Operations;

- In the absence of the Manager of IRB Operations, assist with the execution of his/her duties outlined above.

### 3.5.3 IRB Office Staff

The primary function of the IRB office is to support the function of the IRB. The Manager of IRB Operations shall allocate day-to-day responsibilities within the IRB office to ensure completion of responsibilities that include, but are not limited to, the following:

- Protocol and all document intake, protocol login to the IRB database, and preliminary review to determine if the protocol may qualify for exempt status or expedited review;

- Preliminary screening of the protocol, associated IRB forms, and supporting documentation to determine if all information required for review is present;

- Preliminary review of informed consent form(s) (ICF) to determine if all of the required elements of informed consent are present as necessary to promote comprehension and accuracy;

- Preliminary assessment of protocols and ICF(s) to determine if regulatory, ethical, and/or legal issues are raised that may require attention and action by the PI prior to review by the IRB;

- For previously reviewed and/or approved studies, intake an processing of all study-related correspondences, serious adverse event reports, unanticipated event reports, amendment requests, continuing review applications, and the processing of such materials in accordance with IRB policies and procedures;
Transmission of a courtesy reminder to the PI regarding continuing review submission;

Maintenance of complete, accurate, and organized IRB files;

With the Institutional Officials, maintain the Massachusetts Controlled Substances Researcher Registration required by the Massachusetts Department of Public Health;

Provide customer service, be responsive and courteous to all those who interface with the IRB.

3.5.3.1 IRB Meeting Minutes

In accordance with 45 CFR 46.115(a)(2) and 21 CFR 56.115(a)(2), formal minutes will be prepared after each IRB meeting. The content of the minutes will be set forth in sufficient detail to provide, among other, the following information:

- Meeting attendance — includes members, ex-officio members, and non-members;
- The time the meeting began and ended;
- Actions taken;
- The basis for requiring changes in or disapproving research;
- A written summary of the discussion of controverted issues and their resolution;
- Specific regulatory findings (e.g., vulnerable populations, off-label use, non-significant risk);
- The votes (for, against, and abstaining) for each agenda item;
- Recusals of IRB members or guests due to potential conflict of interest; and
- Whether any proposed changes constitute substantive changes and require re-review by the convened IRB for approval, or whether the changes are not substantive and may be reviewed and verified via expedited review by the IRB Chair/an IRB Vice-Chair, or designee.

A recording may be made of each meeting to facilitate the preparation of written minutes. If a recording is made, upon IRB vote to approve the meeting minutes, recordings of the meeting will be discarded. The minutes of each meeting must be prepared and available to all members of that committee in sufficient time prior to the next meeting to allow for members’ review. The minutes will be transmitted electronically (e.g., electronic mail or posted to the secure institutional IRB wiki website).

A vote shall be taken at each meeting regarding the IRB approval of the minutes from the previous meeting. Proposed modifications to the minutes must be voted on by the IRB. Such modifications will be recorded by the IRB Coordinator and the minutes revised accordingly for the IRB files. Only those members who attended the meeting in question may suggest modification to, and vote on, the minutes.

3.5.4 IRB-RED and IRB-BLUE

The Tufts MC and TUHS IRB is a dual system, comprised of two (2) committees that are comprised of the following:

- Chair
Each IRB(s) shall meet monthly. Typically the meeting time will not change during the calendar year, unless an extenuating circumstance arises. The IRB may meet on a more frequent basis to accommodate the volume or complexity of research. The proceedings and discussions at a convened IRB meeting shall be held in the strictest of confidence.

3.5.4.1 Conflicts of Interest

In conformity with 45 CFR 46.107(e) and 21 CFR 56.107(e), no member may participate in any review activities of any research in which the member has a potential conflicting interest, except to provide information as requested by the IRB. Usually, such members will be present only for the presentation and discussion of this research, and then only to provide clarification that enhances the IRB’s ability to protect human subjects. At the IRB Chair’s discretion, potentially conflicted members may be recused from the presentation or discussion as well.

The member will be required to leave the room for the deliberation and vote. A member who is the PI, a Co-investigator, recruits to the study, or has a potential or perceived conflict of interest in the research will be excused from the room during the deliberation and vote. Such recusals extend to the IRB Chair, IRB Vice-Chairs, IRB management and staff, as well as any other non-voting observers. Upon request, the IRB office will supply a member with formal verification of his/her recusal. In addition, any non-member present who has a potential conflicting interest with any item on the agenda will be asked to leave the room for the deliberation and vote.

3.5.4.2 Utilization of Outside Expertise

If, at any time, the IRB reviews a protocol requiring expertise beyond, or in addition to, that available on the IRB, the IRB may invite individuals with experience in such areas to serve as non-voting consultants. A motion to involve a consultant may be made by any member in attendance at the convened meeting; however, the utilization of a consultant must be made by majority vote of the members present. A consultant may also be engaged at the discretion of the IRB Chair prior to initial presentation of a protocol.

3.5.5 The IRB Chair

The IRB Chair presides over IRB meetings and has such other duties as are identified in this manual. The Chair will be appointed by the Institutional Officials and must have demonstrated an understanding of the regulations governing human subject research, awareness of the ethical considerations raised by such research, and a commitment to the highest standards of research integrity and human subject protection.

The IRB Chair is required to schedule time to report to the IRB office at least twice weekly to review submissions via expedited review procedures, address potential non-compliance issues, etc. The required weekly in-office time allotments of the IRB Chair will be commensurate with the percentage of time arranged with the individual’s Department/Division and will be determined by the necessity of his/her presence. The IRB Chair will receive salary support for his/her work. The percentage will be determined based on agreement between the Institutional Officials and the Chair.
The IRB Chair has the following responsibilities, among others:

- Chair IRB meetings, or delegate the responsibility to an IRB Vice-Chair or designee, as necessary.
- Be a resource to provide recommendations, education, guidance, and mentorship to Primary and/or Secondary Reviewers;
- Serve as the Executive Committee Chair;
- With the Institutional Officials and the Manager of IRB Operations, develop, provide input on, and carry out policies and procedures necessary to maintain or enhance the function of the IRB and protections of human subjects;
- Be a resource to, and to enhance communication between, investigators and the IRB;
- Provide recommendations and nominations of new IRB members;
- Provide recommendations and nomination for the appointment of Vice-Chairs;
- Consult with the Institutional Officials and the Manager of IRB Operations regarding the composition of the IRB as necessary to ensure adequate and efficient reviews and performance;
- Act as a signatory for IRB correspondence;
- Provide review and determination regarding:
  - Certification of exemption from 45 CFR 46
  - Expedited review of research per 45 CFR 46
  - Amendment or modification to research during a study’s approval period, and other submissions provided by investigators
  - Serious Adverse and Unanticipated Events
  - Response(s) to IRB requests
  - Emergency use review
  - Potential research non-compliance
  - Request for waiver of HIPAA research authorization
  - Request for HIPAA review preparatory to research
  - Notices of voluntary closure to accrual, suspension, and termination
- Act as a Primary or Secondary Reviewer of research presented to the convened IRB;
- The IRB Chair must complete all mandated human subject protection education requirements and is expected to participate in periodic research education teaching activities.
- Act in accordance with all institutional research policies.

### 3.5.6 The IRB Vice-Chairs

Each committee will have an appointed IRB Vice-Chair(s). The IRB Vice-Chairs will typically be chosen from the experienced members of the IRB.
The IRB Vice-Chairs are required to schedule time to report to the IRB office on a weekly basis to review submissions via expedited review procedures, address non-compliance issues, etc. IRB Vice-Chairs will be expected to return to the IRB office in a timely manner (i.e., within the same week) to sign follow-up correspondence to PIs. The required weekly time allotment of an IRB Vice-Chair will be commensurate with the percentage of time arranged with the individual’s Department/Division and will be determined based on the volume of information to be reviewed by the IRB Vice-Chairs. Each IRB Vice-Chair will receive salary support for his/her work. The percentage will be determined based on agreement between the Institutional Officials and the IRB Vice-Chair.

The duties of the IRB Vice-Chair(s) reflect the duties of the IRB Chair. The IRB Vice-Chairs fulfill these duties as designated by the IRB Chair.

The IRB Vice-Chairs have the following responsibilities, among others:

- Assist the IRB Chair in the performance of his/her duties, including officiating at convened IRB meetings, as needed;
- Serve as members of the Executive Committee;
- Each IRB Vice-Chair must complete all mandated human subject protection education requirements and are expected to participate in periodic educational activities as defined by the Chair;
- Provide recommendations for potential new IRB members;
- Provide recommendations for potential IRB Vice-Chairs, as requested;
- Consult with the Institutional Officials, the Chair, and/or the Manager of IRB Operations regarding the makeup of the IRB as necessary to ensure adequacy and efficiency of reviews;
- Act as a signatory for IRB correspondence;
- Act as a Primary or Secondary Reviewer;
- Provide review and determination regarding
  - Certification of exemption from 45 CFR 46
  - Expedited review of research per 45 CFR 46
  - Amendment or modification to research during a study’s approval period, and other submissions provided by investigators
  - Serious Adverse and Unanticipated Events
  - Response(s) to IRB requests
  - Emergency use review
  - Potential research non-compliance
  - Request for waiver of HIPAA research authorization
  - Request for HIPAA review preparatory to research
  - Notices of voluntary closure to accrual, suspension, and termination
- Act in accordance with all institutional research policies.
3.5.7 IRB Members

The time of initial appointment for each new IRB member will be 1 year. Members will be re-evaluated by the Institutional Officials, the IRB Chair, and the Manager of IRB Operations at the time of reappointment, but, a term limit will not be imposed.

IRB Members have the following responsibilities, among others:

- New members will undergo orientation by a trained IRB Coordinator, in consultation with the IRB Chair, and the Manager of IRB Operations, and may, based on a determination by the IRB Chair, observe the proceeding(s) of a convened IRB meeting(s) for a period of time. Orientation conducted by the IRB Coordinator will be documented.

- Complete all mandated human subject protection education requirements prior to serving as a voting member of the IRB and complete ongoing training on an annual and/or more frequent basis, as needed.

- Review materials on the IRB agenda and participate in the discussion of the studies at the convened IRB meeting. Materials will typically be distributed to members (i.e., made available to IRB members via the secure institutional IRB wiki), including the Institutional Officials and Manager of IRB Operations, at least seven (7) calendar days before the meeting. Circumstances may arise whereby materials are forwarded to IRB members fewer than seven (7) calendar days prior to the meeting, e.g., addendum to the agenda, revised or additional materials provided by the PI. The agenda will be comprised of each research proposal and related documents (including ICFs, Investigator’s Brochure if applicable, recruiting information, etc.).

- Review the complete IRB file of the protocols(s) she/he is assigned to review at the convened IRB meeting. Members are encouraged to do this when reviewing amendment and continuing review submissions to be presented to the convened IRB. The Reviewer may contact the IRB office to arrange a time to review the pertinent file(s) in advance of the IRB meeting. A complete copy of the IRB file for all studies on an agenda is available in the IRB office for review by IRB members prior to a meeting.

- Information Required for New Study Review

For new studies, each IRB member will receive a copy of the following minimum information submitted by investigators or generated by the IRB Coordinator approximately seven (7) days prior to any IRB meeting:

- Protocol
- Site-specific appendix
- IRB Forms
- Proposed ICFs
- Drug(s), compound(s), and/or device information
- Copy of the grant supporting the research, if applicable
- All written information containing materials provided to subjects including, but not limited to, telephone script(s), interview text, questionnaire(s), survey instrument(s), advertisement(s), and contact letter(s).
• Recruitment materials (letters, advertisements, postings, e-mail announcements, etc.)
• HIPAA documentation.

Information Required for Continuing Review

Each IRB member will receive a copy of the following minimum information before any study is presented to the convened IRB for continuing review:

• Form V
• Approved ICFs

Information Required for IRB Notification

Each IRB will receive notification of the following events in a monthly compilation:

• Exempt status certifications
• Expedited initial review approval
• Expedited Continuing Review approval
• Expedited modification/amendment approval
• Emergency use review
• Non-compliance
• Involuntary suspension or termination actions taken by the IRB Chair
• Any event deemed reportable to a regulatory Department or Agency
• Any other information as deemed necessary by the Chair.

Each member will be assigned to one IRB (e.g., Red or Blue). Only the IRB Chair will be a voting member of both IRBs. Each member is expected to attend at least ten (10) of the twelve (12) scheduled IRB meetings during the calendar year. Members are expected to remain throughout the duration of the entire meeting, except in the event of a potential COI, and are expected to actively participate in the discussion of research presented to the IRB. Only those members who attended a meeting in question may amend and vote on the meeting minutes.

Each member will be expected to conduct initial reviews of research and/or continuing reviews and/or modifications to approved research and present them to the convened IRB along with recommendations for approval, modification, or disapproval. Assignments will take into account each member’s expertise and experience. Each member will also be expected to serve as a Secondary Reviewer of research, as assigned. The focus of the Secondary Reviewer will be the review of the ICF, including readability and accuracy.

To facilitate a timely and complete review, members are strongly encouraged to communicate with the PI (or designee) of a given research study for which she/he is assigned to review to request clarification or verification. Communication with the PI should occur prior to the meeting so that the review process may continue as scheduled. Members are expected to provide a copy of any electronic mail exchanges, as it pertains to the study under review, or a written summary of any meeting/telephone conversation. Members are expected to provide a summary of salient issues discussed, as they pertain to the research under review.
At the IRB meeting, each protocol shall be individually reviewed and discussed as the IRB Coordinator/Continuing Review Coordinator records information for the minutes. The IRB will decide upon one of the following actions by a majority vote of the members present:

- Approval
- Approval with Stipulation(s)
  - Substantive changes
  - Not substantive changes
- Deferral
- Disapproval
- Tabled
- Withdrawn

It is the Primary Reviewer responsibility, with help from the IRB Chair and IRB Coordinator, to assure that the PI’s submission offers sufficient information to enable the IRB to make an informed judgment about whether and under what conditions to approve the protocol. In the event that the protocol and/or ICF(s) raise(s) issues that the IRB requires additional information or clarification, the Primary Reviewer is to contact the PI or his/her designee prior to the meeting to obtain the necessary additional information or clarification and corresponding revised documents, as indicated.

One week before the IRB meeting, an agenda comprised of each research proposal, and related documents (including the ICF, recruiting information, etc.) will be distributed to members, as well as the Institutional Officials and the Manager of IRB Operations.

The Primary Reviewer shall receive all of the materials listed above approximately seven (7) days before the date of the meeting, or sooner if available sooner. If applicable, the Primary Reviewer will also be provided with any federal grant(s) or funding application(s) to verify that the proposed research is within the scope of the grant(s)/application(s) stated aims.

A Secondary Reviewer will be assigned to review a protocol submitted for initial review. Prior to the IRB meeting, the Secondary Reviewer is to carefully review the ICF(s) together with the protocol and any other related documentation to ensure that the ICF(s) accurately reflect the study procedures in the protocol, is of sufficiently simple readability, and contains all of the required elements of informed consent. The Secondary Reviewer will be given a checklist to complete to help ensure that the required elements of consent are present.

It is the responsibility of the Primary Reviewer to attend the IRB meeting with a complete, type-written presentation/summary of a study describing any suggested changes to the protocol, ICF(s), or other research study instruments used in the study. To aid in the presentation, the Primary Reviewer is encouraged to prepare a visual presentation; appropriate audiovisual equipment will be available at IRB meetings. If ICF revisions will be recommended, the Primary and/or Secondary Reviewer is to provide a notated ICF or a separate document detailing the specific changes required.

The Primary Reviewer is responsible for leading the presentation and discussion of the research at the IRB meeting. The Primary Reviewer will also make recommendations regarding approval, modification, deferral or disapproval of the protocol, as well as any suggested revisions to the ICF(s), etc. The Primary Reviewer will also make a recommendation whether the recommended changes are substantive in nature and require re-review by the convened IRB, or are not substantive in nature and may be reviewed and
verified via expedited review. These recommendations are presented in the form of a motion that is seconded and voted on at the meeting.

In the event that a Primary Reviewer is unable to attend a meeting, he/she is responsible for providing a detailed written summary of the study, potential issues of concern for discussion, if any, and his/her recommendations for IRB action to the IRB Chair, who may at his/her discretion present it at the IRB meeting.

In the event that a PI requests that the IRB reconsider a stipulation, the original/most recent Primary Reviewer will present the request for reconsideration at a convened meeting of the IRB that voted for the stipulation (see section 4.3.10, Request for Reconsideration). In the event that a prior Primary Reviewer is not available, the IRB Chair will present the protocol him/herself or may appoint a new Primary Reviewer.

The IRB leadership will provide Reviewer forms to IRB members to help ensure that the required elements of review are documented/presented. The Primary Reviewer is expected to complete the requisite review form, sign it, and at the conclusion of the IRB meeting leave it for the IRB Coordinator. The Secondary Reviewer is similarly expected to complete the requisite review form, sign it, and at the conclusion of the IRB meeting leave it for the IRB Coordinator.

Subsequent to the meeting, the Primary and Secondary Reviewer is responsible for reviewing the portion of the minutes of that meeting that pertain to the protocol(s) that he/she presented/reviewed, and for requesting any changes in the minutes that may be necessary to ensure accuracy.

3.6 Ex-Officio Members

Holders of specific offices, not individuals, will be appointed as non-voting ex-officio members of the IRB. Ex-officio members will be appointed in recognition of their expertise and mission as it relates to the institutions’ human research programs. These ex-officio members will be non-voting members. The person holding the following offices will be non-voting ex-officio members of the IRB:

- Tufts University Vice Provost
- Tufts MC Vice-President of Research Administration
- Manager of IRB Operations

3.7 Scientific Review Committee (SRC)

3.7.1 Purpose

The SRC was established to reinforce the institutional mission in promoting research excellence. The SRC will review selected clinical research proposals submitted to the IRB to ensure that they meet an acceptable standard of scientific rigor and merit prior to IRB review.
3.7.2 Criteria for Selection

The SRC routinely reviews greater than minimal risk protocols submitted for review by the convened IRB. The basic requisite for requiring SRC review is a protocol that has not previously undergone an independent peer review process. The types of protocols that fall under this category are usually investigator initiated, from a single site pharmaceutical company sponsored studies, or early phase clinical trials.

Prior to initial review by the convened IRB, the SRC will routinely review greater than minimal risk research protocols except the following:

- Research approved for federal funding (e.g., DoD, DoE, DoJ, EPA, HHS, AHRQ, CDC, FDA, NIH, etc.)
- Research approved for corporation/foundation/organization/association funding utilizing an adequate peer review mechanism, as determined by the SRC Chair
- Research that qualifies for expedited IRB review
- Research that qualifies for exemption from IRB review
- Research that poses minimal risk to human subjects.

The IRB and/or the Institutional Officials may, at their discretion, forward any protocol to the SRC at any point during the review process.

3.7.3 SRC Process

- A study PI submits a new study application to the IRB office.
- IRB staff performs a preliminary assessment of the submission to determine whether it meets the criteria for assessment, including if the protocol has undergone prior scientific review.
- The protocol is forwarded to the SRC Chair, as needed, for final determination of whether institutional SRC review is required and if an expert content reviewer is required. These decisions are noted in the IRB study file.
- If SRC review is indicated, a SRC meeting will be scheduled. To achieve a quorum of the SRC, there must be two (2) medical reviewers and 1 statistical reviewer present. If the quorum is cannot be maintained, the meeting will be stopped until a quorum can again be achieved.
- The SRC Chair assigns a medical and a statistical reviewer to each protocol that is being reviewed. If necessary, an expert content reviewer will also be assigned to review the protocol (see Expert Content Reviewer section below).
- The deadline for each SRC meeting is that the protocol must have been submitted to the IRB office at least three (3) business days prior to the SRC meeting. This deadline may be shortened at the discretion of the SRC Chair to accommodate receipt of responses to prior SRC comments, provided that there is adequate time for the SRC members to review the responses prior to the meeting.
- All protocols scheduled for review are made available to the SRC members at least three (3) business days prior to the meeting via the secure institutional IRB wiki.
3.7.4 Actions by the SRC

Based on the review of the proposed research the SRC may vote to take either of the following actions:

- Protocol is forwarded to the IRB
- Protocol is returned to the PI for further action.

3.7.5 SRC Correspondence

- The SRC Coordinator drafts the initial letter that will be sent to the PI.
- The SRC Coordinator e-mails the letter to the SRC Chair and the Primary Reviewers for them to edit/revise.
- The final letter is typically mailed to the PI within 1 week of the SRC meeting and sent to the PI and SRC members via email.
- The Department Chair/Division Chief should receive a copy of the letter that was forwarded to the PI.
- Notes of SRC meetings will be recorded to assist with the preparation of the review letters; notes may only be access by the Institutional Officials, IRB office staff, and members of the SRC and IRB. Formal meeting minutes of SRC meetings are not created.

3.7.6 Responses to SRC Reviews

- If the protocol was returned to the PI for further action, the PI may submit a response and revised protocol to the SRC for review.
- The PI submits the response to the IRB office. The SRC Coordinator forwards the response, revised documents, and the original SRC letter to the SRC Chair and the two (2) SRC reviewers. The SRC reviewers and the SRC Chair determine if the material is acceptable or if it needs to be discussed at the next convened SRC meeting.
- The PI is informed by letter of the SRC’s review of the response/determination, which is also sent to the PI and SRC members via email.
- If appropriate, the SRC may require further action by the PI. Correspondence will be forwarded to the PI requesting further action. The PI may revise the protocol per the SRC comments and re-submit for review.
- At any time during this process, the PI may contact the SRC Chair for assistance. This is clearly documented in the letter that is forwarded to the PI.

3.7.7 Content Expert Reviewers

During the course of conducting its review of proposed protocols, the SRC may need the assistance of members of the faculty or other expert reviewers who possess specific expertise relevant to the disease or
condition in question. These questions may concern the relevance of the proposed study to the field or other technical issues beyond the expertise of the committee members. The role of the expert reviewer would be to address specific questions posed by the SRC. Expert reviewers will not be expected to provide written comments.

When this need is identified, either by the SRC Chair, the SRC medical reviewer in consultation with the SRC Chair or by the SRC itself, the SRC Chair or his/her designee will contact the Division or Department head and ask for his/her assistance in identifying a willing and available expert. The Division or Department head is responsible for identifying and contacting the expert reviewer. The SRC Chair should contact the expert to verify that she/he:

a. Possesses the requisite expertise.
b. Is not a research team member on the protocol subject to review.
c. Is available to perform the review in a timely manner.
d. Is willing to undertake the task.

The SRC Chair should document the above points in the study file.

If identifying an expert reviewer results in a delay of more than 1 week, the PI will be notified by the SCR Chair that the protocol will be delayed until an expert reviewer has been identified. Once the expert has been identified, the SRC will invite the expert to attend its next meeting, at which time the protocol will be discussed. The SRC recommendation will be transmitted to the PI in a hard copy letter and to the PI and SRC members via email.

### 3.7.8 Process for Contacting Content Expert Reviewers (all departments except for Hematology/Oncology)

- The SRC Chair or his/her designee or the SRC Coordinator will send an e-mail to the Division or Department head requesting that he/she identify a content expert for the protocol.
- The Metabolic Research Unit Manager at the HNRCA is responsible for identifying content expert reviewers for HNRCA studies.
- Once a content expert reviewer has been identified, the SRC coordinator will coordinate with the reviewer to schedule attendance at the SRC meeting.
- The SRC Chair will assign the SRC medical and statistical reviewer for the protocol.

### 3.7.9 Process for Contacting Content Expert Reviewers for Hematology/Oncology

- Per the request of the Chair of the department of Medicine at Tufts MC, all protocols from the Division of Adult Hematology/Oncology require 2 content expert reviewers. If an hematologist/oncologist is a member of the SRC, she/he may serve this purpose. If additional reviewers are necessary, the Division of Hematology/Oncology is required to identify the additional necessary content expert reviewers for each protocol.
- The SRC Chair or his/her designee or the SRC coordinator will send an e-mail to the Senior Research Administrator in the Division of Hematology/Oncology requesting 1 or more content expert reviewer(s).
- The Senior Research Administrator will notify the SRC Coordinator once a reviewer has been identified. The SRC Coordinator will coordinate with the reviewer in scheduling the meeting and review.
3.8 Western IRB (WIRB)

Protocols conducted at Tufts MC / TUHS that meet the following criteria are eligible for submission to WIRB:

1. Industry sponsored or non-federally funded foundation sponsored
2. Multi-Center
3. Sponsor initiated (defined as sponsor created, designed, and developed)
   - If the study involves research on an FDA regulated test article, it meets one of the following criteria:
     a. Drugs, Biologics, Substances: Study is in Phase II, III or IV (Phase I studies are NOT eligible)
     b. Devices: Study is in pivotal, post-marketing, or equivalent, phase (Pilot or first-in-man studies are NOT eligible)

A PI may choose to submit a study that meets these criteria to either the Tufts MC/TUHS IRB or WIRB, not both. If the study has previously been reviewed by the Tufts MC/TUHS IRB, then it is not eligible for submission to WIRB. The institutions, Tufts MC and Tufts University, cannot approve any research study that has been disapproved by WIRB. WIRB review would be performed in place of the Tufts MC/TUHS IRB review performed by the convened IRB. There is no obligation to use WIRB.

Studies that will be reviewed through the WIRB-Copernicus Single Review Solution (SRS) are eligible for submission to WIRB if they meet the above criteria. If a study is submitted as part of the WIRB-Copernicus SRS, a WIRB application must be completed and submitted directly to WIRB (www.WIRB.com). WIRB will provide an approval letter – Do NOT submit the application to the Copernicus Group IRB or the WIRB-Copernicus Group.

If the study involves a test article that has been issued an IND or IDE number, in order for the study to be eligible for submission to WIRB, the IND or IDE number must be issued to the sponsor of the study and not an investigator. If a determination must be made by the IRB regarding the need for an IND or IDE for a test article (21 CFR 312 or 21 CFR 812) the study will not be eligible for submission to WIRB. Arrangements for sub-sites under a Tufts MC or TUHS primary site are the responsibility of the PI to pursue separately with WIRB, independent of his/her relationship with Tufts MC or TUHS. Tufts MC and TUHS reserve the right to allow or deny any study submission to WIRB.

3.9 National Cancer Institute (NCI) Central IRB (CIRB)

3.9.1 NCI CIRB Background

Tufts Medical Center and the Floating Hospital for Children participate in the independent (pilot) model of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) Initiative. Under this model, the Adult and Pediatric CIRBs are the IRBs of record for certain adult and pediatric national multi-center cooperative oncology group cancer treatment trials.
Tufts Medical Center provides information about local context to the CIRBs. The CIRBs assume responsibility for initial review, continuing review, modifications to approved research, unanticipated problems and non-compliance. Tufts Medical Center’s role in this process is to oversee the local conduct of the research. This responsibility is shared with the Departments/Divisions conducting the research and the Neely Center for Clinical Cancer Research (NCCCR). The Tufts MC / TUHS IRB has access to the current list of protocols reviewed by the CIRBs and acts as a resource to the NCCCR.

The CIRB Initiative is sponsored by the National Cancer Institute in consultation with the Department of Health and Human Services Office for Human Research Protections (OHRP). The Tufts MC / TUHS IRB functions as a liaison between the CIRB and the investigators, and as a resource to investigators, when needed. The Tufts MC / TUHS IRB completes the Annual Institutional Worksheet, which apprises the CIRBs of local context, includes required informed consent template language, applicable local and State regulations, and Tufts MC / TUHS IRB policies. Investigators submit an Annual Investigator Worksheet for each investigator, and a Study-specific Worksheet for each study in which they wish to enroll participants, directly to the CIRB. The CIRB is responsible for continuing review, review of subsequent modifications, non-compliance, and unanticipated problems. CIRB copies the Tufts MC / TUHS IRB on notices when studies are initiated or closed. Investigators copy the Tufts MC / TUHS IRB on reports of local non-compliance, and unanticipated problems, and report these directly to CIRB on forms designed for this purpose.

Division of Responsibilities (as described in the IRB Authorization Agreement)

The responsibilities of the NCI CIRB are to:

1) Maintain an NCI CIRB membership that satisfies the requirements of 45 CFR 46 and 21 CFR 56 and provides special expertise as needed to adequately assess all aspects of each study;
   a) Post the roster of NCI CIRB membership on the public side of the NCI CIRB website;
2) Conduct initial, amendment, and continuing review of studies as well as review of any other study-specific documents submitted by the Study Chair to the NCI CIRB;
3) Conduct review of local context considerations:
   a) as outlined in the following Worksheets: the Annual Signatory Institution Worksheet About Local Context for NCI CIRB Review, the Annual Principal Investigator Worksheet About Local Context, and the Study-Specific Worksheet About Local Context;
4) Conduct review of potential unanticipated problems and/or serious or continuing noncompliance when the Signatory Institution or other entity reports an incident, experience, or outcome to the CIRB. This review includes the following step:
   a) report any unanticipated problem and/or serious or continuing noncompliance determination to OHRP, the FDA, and the NCI Signatory Official;
5) Conduct review of individual Adverse Event Reports for studies without a Data and Safety Monitoring Board (DSMB) or equivalent monitoring body;
6) Post all study-specific documents related to CIRB reviews to the restricted access side of the CIRB website;
   a) Notify research staff and institutional designees of all CIRB actions, per written procedures, via institution-specific correspondence, broadcast emails, and access to the restricted area of the CIRB website;
7) Notify the Signatory Institution immediately if there is ever a suspension or restriction of the CIRB’s authorization to review a study; and
8) Post the NCI CIRB Standard Operating Procedures on the public side of the CIRB website.

The responsibilities of Tufts Medical Center are to:
1) Comply with the NCI CIRB’s requirements and directives;
2) Report to the NCI CIRB the names of any Component or Affiliate Institutions that rely on the Signatory Institution’s IRB.
   a) Component Institutions are defined by the NCI CIRB as meeting all of the following criteria:
      i) the Component Institution operates under a different name than the Signatory Institution, but the Signatory Institution has legal authority for the Component Institution;
      ii) the FWA number for the Component Institution is the same as the Signatory Institution;
      iii) the local context considerations of the Component Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context;
      iv) the boilerplate language and institutional requirements of the Component Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and
      v) the conduct of research at the Component Institution is monitored by the same office as the Signatory Institution.
   b) Affiliate Institutions are defined by the NCI CIRB as meeting all of the following criteria:
      i) the local context considerations of the Affiliate Institution are the same as the Signatory Institution. Local context considerations are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context;
      ii) the boilerplate language and institutional requirements of the Affiliate Institution are the same as the Signatory Institution. The boilerplate language and institutional requirements are reported by the Signatory Institution in the Annual Institution Worksheet About Local Context; and
      iii) the conduct of research at the Affiliate Institution is monitored by the same office as the Signatory Institution.

3) Ensure the safe and appropriate performance of the research at the Signatory Institution and at all Components and Affiliates. This includes, but is not limited to:
   a) ensuring the initial and ongoing qualifications of investigators and research staff;
   b) overseeing the conduct of the research;
   c) monitoring protocol compliance;
   d) maintaining compliance with state, local, or institutional requirements related to the protection of human subjects;
   e) providing a mechanism to receive and address concerns from local study participants and others about the conduct of the research; and
   f) investigating, managing, and providing notification to the NCI CIRB of any study-specific incidence, experience, or outcome that seems to rise to the level of an unanticipated problem and/or serious or continuing noncompliance. When notifying the NCI CIRB of a potential unanticipated problem and/or serious or continuing noncompliance, the institution must provide a plan to manage the incident, experience, or outcome, including measures to prevent similar occurrences;

   NOTE: As part of ensuring safe and appropriate performance of research the Signatory Institution has the authority to observe any aspect of the research process including observing the consent process. The CIRB retains the authority to direct this to be done when necessary.

4) Provide updates in a timely manner to the NCI CIRB whenever a Signatory Institution Principal Investigator is no longer the responsible party for a study under the purview of the NCI CIRB;
5) Notify the NCI CIRB when a regulatory deficiency has been cited on an audit that occurred during the time that the NCI CIRB was responsible for study review;
6) Complete and submit the Annual Institution Worksheet About Local Context, the Annual Investigator Worksheet About Local Context, and any other worksheets/forms required by the NCI CIRB for participation;
7) Decide on a study-by-study basis whether to open the study through the NCI CIRB or to conduct its own local IRB full Board review. Indicate the decision to open a study through the NCI CIRB by submitting a Study-Specific Worksheet About Local Context;

8) In the local consent form:
   a) incorporate NCI CIRB-approved boilerplate language into the NCI CIRB-approved model consent form;
      NOTE: Including HIPAA Authorization language as part of boilerplate language is permitted. The CIRB does not approve the HIPAA Authorization language as it does not function as a Privacy Board however the CIRB will accept HIPAA Authorization language when submitted as part of the boilerplate.
   b) make no language changes to the consent form with the exception of NCI CIRB-approved boilerplate language;
   c) obtain NCI CIRB approval of changes to the boilerplate language prior to implementation; and
   d) obtain NCI CIRB approval of translations of the consent form prior to implementation;

9) Maintain a regulatory file for each study under NCI CIRB purview as per local institution and sponsor policy; and

10) Conduct full board review of any study enrolling prisoners, since the NCI CIRB is not constituted to review studies enrolling prisoners.
4 Operations and Procedures

The IRB(s) shall meet monthly. The IRB(s) may meet on a more frequent basis to accommodate the volume or complexity of research. The proceedings and discussion at a convened IRB meeting are to be held in the strictest of confidence.

The Institutional Officials, in consultation with the Executive Committee, may decide to increase or decrease the number of IRBs as necessary to ensure the adequate and efficient review of the submitted research.

Four (4) types of review can be applied to new research study applications (not human subject research, exempt, expedited, review by the convened IRB). None of the types of review is superior or inferior to the other. The type of review is strictly dependent on the research study design and the nature of the research.

This section discusses the following types of operations and review procedures:

- Not Human Subject Research
- Determination of Exempt Status
- Initial Review
  - Expedited
  - Convened IRB review
- Continuing Review
  - Expedited
  - Convened IRB review
- Modification of Previously Approved Research
  - Expedited
  - Convened IRB review
- Emergency use review

All human research that is not deemed by federal regulations to be exempt from IRB review (i.e., 45 CFR 46.101) is subject to initial and continuing review either (1) by a convened meeting of the IRB or (2) by expedited review procedures, if eligible under applicable regulations.

After initial IRB review and approval investigators are expected to submit/report the following to the IRB:

- Continuing review (except studies granted exemption)
- Amendments/changes in research activity
- Unanticipated problems
- Serious adverse events
- New information that may affect a subject’s willingness to continue participation
- Deviations from the protocol
- Monitoring reports
- Non-compliance
4.0 Not Human Subject Research

In accordance with guidance issued by the Office for Human Research Protections, revised on 16 October 2008, *Guidance on Research Involving Coded Private Information or Biological Specimens*, certain projects involving coded private information or human biological specimens that is conducted or supported by HHS may be determined to not be research involving human subjects. This determination will be made by the IRB Chair, Vice-Chair, or designee and communicated in writing to the PI.

Per OHRP policy, under certain limited conditions, research involving only coded private information or specimens is not human subject research.

Some HHS conducted or supported research involving coded private information or specimens may be subject to Food and Drug Administration (FDA) regulations. The FDA regulatory definitions of human subject (21 CFR 50.3(g), 21 CFR 56.102(e)) and subject (21 CFR 312.3(b), 21 CFR 812.3(p)) differ from the definition of human subject under HHS regulations at 45 CFR 46.102(f). In accordance with the guidance document, the IRB may not apply the guidance to research regulated by FDA that involves coded private information or specimens.

When assessing whether or not projects involving coded private information or human biological specimens constitute research involving human subjects, per the HHS guidance, coded will mean that (1) identifying information (such as name or social security number, etc.) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human subject at 45 CFR 46.102(f), obtaining/receiving identifiable private information or identifiable specimens for research purposes constitutes human subject research.

In accordance with OHRP guidance, the IRB will consider private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, per OHRP, the IRB will not consider research involving only coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met: (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and (2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example: (a) the key to decipher the code is destroyed before the research begins; (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This policy applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for
purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

4.1 Determination of Exempt Status

In accordance with the provisions of 45 CFR 46.101(b) and 21 CFR 56.104, some human subject research may be exempt from the application of applicable regulations. However, under no circumstances is the PI to determine the exempt status of his/her research; the Tufts MC/TUHS IRB requires that all research involving human subjects must be submitted for review, regardless of the possibility of exemption.

A decision to grant exempt status will be made by the IRB Chair, a Vice-Chair, or designee and communicated in writing to the PI.

4.1.1 Form(s) and Process for Determining Exempt Status

For research that meets the regulatory requirements of exemption, the PI is to submit a signed Request for Exemption form along with a copy of the proposed research protocol. The PI must also provide a statement as to the applicability of HIPAA. In addition, a copy of any grant, questionnaires, advertisements, etc., that correspond to the research is to be submitted to the IRB for review. Form VII, as discussed elsewhere in this manual, may be submitted instead of the Request for Exemption form for medical record or clinical database research for which an exemption is sought.

Requests for exemption will be pre-reviewed for completion, accuracy of submission, etc., by an IRB office staff member. The application will then be forwarded to the IRB Chair, a Vice-Chair, or designee, for review.

If the research is not granted an exemption from IRB review, the PI will be advised of the need to submit other relevant documents for review by the IRB, as directed by the IRB reviewer.

Research team members engaged in research that is granted an exemption are not required to complete the institutional mandatory human subject research education requirements.

If a project is granted exemption, that determination will be sent to the PI in writing. A project granted exemption would not be required to undergo continuing review; the exempt status of the research will not expire. If the PI proposes to make any change to the project once an exemption is granted the proposed change is to be submitted in writing to the IRB for review to ensure that the study still qualifies for exemption. When an exemption is granted, the PIs will be advised of the need to obtain IRB approval prior to changing the project. The PI will also be instructed to notify the IRB office in writing when the research is terminated to ensure accurate IRB records.

4.2 Initial Review

Research applications that are not eligible for exempt status are required to be reviewed by expedited review procedures or by a convened IRB.

This section contains the following information concerning expedited and convened IRB review:
4.2.1 Expedited Review

In accordance with federal regulations 45 CFR 46.110 and 21 CFR 56.110, some research\textsuperscript{9,10,11} may be reviewed and approved through expedited review procedures at the time of initial review. It is noted that FDA regulation does not include research on behavior or characteristics of groups or individuals such as studies of perception, cognition, game theory, or test development (45 CFR 46.110(b)(9)) in its list of research activities that may be reviewed through expedited review procedures, because the FDA does not regulate those types of studies.

Expedited review procedures may be used when the proposed research involves no more than minimal risk as defined by federal regulation. A decision to use expedited review procedures will be made by the IRB Chair, a Vice-Chair, or designee. Use of expedited review procedures allows the IRB Chair, a Vice-Chair, or the designee to exercise the authority of the convened IRB, therefore not requiring the research to be presented at a convened meeting of the IRB. However, the IRB Chair, Vice-Chair, or the designee may not use expedited review procedures to disapprove a study; such an action can only be taken by the convened IRB.

Research that is reviewed by expedited review procedure is evaluated in terms of the same regulatory criteria as research that is evaluated by a convened IRB. The difference between expedited review and convened IRB review is the number of IRB members who participate in the review.

4.2.1.1 Form(s) and Process for Determining Expedited Review

A PI may request expedited review; however, the appropriateness of expedited review will be determined by the IRB Chair, a Vice-Chair or designee. Even if proposed research qualifies for expedited review, the IRB Chair, Vice-Chair, or designee retains the option to forward a request for expedited review to the convened IRB.

\textsuperscript{9} Categories of Research that May be Reviewed by an Institutional Review Board through an Expedited Review
\textsuperscript{10} Office for Human Research Protections (OHRP) Guidance on the Use of Expedited Review Procedures dated 11 August 2003
When seeking initial expedited review, the PI is to submit a signed Form I, a copy of the proposed research protocol, and a statement as to the applicability of HIPAA. Form I collects the information required and necessary to describe the research design to enable a reviewer to evaluate a study. In addition, a copy of any grant, questionnaires, advertisements, etc., that corresponds to the research is to be submitted to the IRB for review. For research that consists only of a medical record or clinical database review the PI may submit a Form VII: IRB Submission and HIPAA Waiver Request. Complete response to questions contained in the Form VII provide the information required and necessary to describe the research design and confidentiality parameters to enable a reviewer to evaluate a study, therefore submitting an independent protocol and HIPAA documentation is unnecessary.

Requests for expedited review may be pre-reviewed for completion, accuracy of submission, appropriateness for expedited review, etc., by an IRB office staff member. If appropriate, the application will then be forwarded to the Chair, a Vice-Chair, or designee for review. The person conducting the review should document the appropriate category for expedited approval and any relevant findings for research on minors, HIPAA, etc.

If expedited review procedures cannot be used, the PI will be advised by the Reviewer or IRB staff of the need to submit any other relevant documents for review by a convened IRB, or if the requisite forms for convened IRB review are already present, the application will be forwarded to an IRB meeting agenda.

Research team members engaged in research that is reviewed and approved using expedited review procedures are required to complete the mandatory institutional human subject research education requirements.

### 4.2.2 Convened IRB Initial Review

All research involving human subjects that is not eligible for exempt status or expedited review will be presented to a convened IRB. The placement of items on an IRB agenda is dictated by the order of receipt and other considerations, such as the number of members scheduled to be present at the meeting. Consideration will be given to extenuating circumstances and will be evaluated on a case-by-case basis by the IRB Chair, Manager of IRB Operations, and the committee IRB Coordinator.

### 4.2.3 Quorum of the Membership

Convened board review takes place at a convened meeting of the IRB at which a quorum for that IRB is present. A majority of the members is required for a quorum; majority is defined as half of an IRB membership plus one.

Per federal regulations, the quorum must include at least one physician/scientist and at least one member whose primary activities are in nonscientific areas. A member who is not present for the deliberation and vote of a particular agenda item may not be counted as part of the quorum with respect to that item. Should the quorum fail during a meeting (e.g., those with conflicts excused, early departures, a non-scientist not present) the meeting will be stopped and no further discussion or votes taken until the quorum is restored.

### 4.2.4 Deliberation and Voting Procedures

The discussion of each agenda item is led by the IRB Chair and the Primary Reviewer, with dedicated presentations given by the Primary Reviewer, and, if applicable, the Secondary Reviewer. At the end of
the discussion, a motion will be made by the Primary Reviewer and a vote taken (for, against, abstention) and recorded by the IRB Coordinator for the meeting minutes. Each study presented for initial review, continuing review, or modification to a previously approved protocol on the IRB agenda will involve an IRB vote and will be presented and voted on separately.

### 4.2.5 Preliminary Review

Upon submission to the IRB office, IRB staff will conduct a preliminarily review of an IRB application for overall completeness. The application will also be reviewed for requisite IRB forms. The level of completeness will determine if the application needs to be (1) returned to the PI or (2) if the PI/the research team should be contacted to obtain missing documents or (3) the IRB review process is ready to begin. All efforts will be made to request missing forms or documents prior to the application being placed on an IRB agenda.

Materials will typically be distributed to all members expected to attend the IRB meeting at least seven (7) calendar days before the meeting. At this time, meeting materials are available to IRB members via a secure institutional wiki website. Addenda to the agenda, revised or additional materials provided by the PI will be forwarded to IRB members as soon as possible. The submitted materials for each research proposal (including ICF, recruiting information, etc.) will be distributed to all IRB members. The IRB Coordinator may notate components of the application with questions, comments, or suggested or preferred language, as appropriate and part of preliminary review, which will be supplied to members.

### 4.2.6 Primary Review

Prior to the IRB meeting, the IRB member assigned to be the primary reviewer will be responsible for carefully reviewing the application. It is the primary reviewer’s responsibility to ensure that the investigator’s submission provides sufficient information to enable the IRB to make an informed judgment about whether, and under what conditions, it may approve the protocol. In the event that the protocol or ICF raises issues that are likely to require further information or clarification, the primary reviewer is strongly encouraged to contact the PI prior to the IRB meeting to obtain the additional information or clarification.

The primary reviewer will also review the ICF(s) together with the protocol to ensure that the ICF(s) contains all of the required elements of informed consent. The ICF must adequately describe the research design and purpose, the procedures to be performed or followed, and if applicable their relationship to standard treatment for the subject’s condition, as well as the risks, benefits and alternatives to participation in the study. It shall be the responsibility of the primary reviewer to come to the IRB meeting with a complete summary describing, in detail, any suggested changes to the protocol, ICF, or other research study instruments being utilized.

The primary reviewer shall be responsible for presenting the protocol to the convened IRB. The primary reviewer is expected to contact the PI prior to the IRB meeting to address and resolve any issues identified during the review. The primary reviewer is also encouraged to employ visual aids as necessary for the presentation (e.g., Microsoft Word or PowerPoint presentation). Necessary equipment will be available at the meeting to display the presentation.

The primary reviewer, with the Chair, will lead the discussion at the IRB meeting. The primary reviewer’s recommendations regarding approval, modification, deferral, or disapproval of the protocol, as well as any suggested revisions to the ICF(s), etc., will be recorded by the IRB Coordinator. If ICF revisions are recommended, the primary reviewer may submit a notated ICF or a separate document detailing the
specific changes required. In the event that the primary reviewer is unable attend the meeting, he/she is responsible for providing a written summary of the study, the issues raised during the review, if any, and his/her recommendations for IRB action to the Chair, who may at his/her discretion present it at the IRB meeting.

Subsequent to the meeting, the primary reviewer shall be responsible for reviewing that portion of the meeting minutes that pertain to the protocol(s) that s/he previously presented/reviewed, and for requesting any changes to the minutes that may be necessary to ensure accuracy.

4.2.7 Secondary Review

A secondary reviewer will be assigned to all studies submitted for initial review. The secondary reviewer’s concentration will be the ICF(s) to ensure that the elements of informed consent are present and accurately reflect the details of the protocol.

If the secondary reviewer recommends ICF revisions s/he may submit a notated ICF or a separate document detailing the specific changes required. In the event that the secondary reviewer is unable attend the meeting, s/he is responsible for providing a written summary of the ICF, and his/her recommendations to the IRB Chair, who may at his/her discretion present it at the IRB meeting.

Subsequent to the meeting, the secondary reviewer shall be responsible for reviewing that portion of the meeting minutes that pertain to the protocol(s) that s/he previously reviewed, and for requesting any changes to the minutes that may be necessary to ensure accuracy.

4.2.8 Actions by the IRB at Initial Review

Except when research is deemed exempt or when an expedited review procedure is used, the IRB will review proposed research applications at a convened meeting at which a quorum of the IRB members are present. Per federal regulations, as applicable (45 CFR 46, 21 CFR 56), research proposals may not be approved unless all of the following criteria for approval are satisfied:

- Risks to subjects are reasonable in relation to anticipated benefits;
- Risks to subjects are minimized;
- Selection of subjects is equitable;
- All required forms, correspondence, and other documents are complete, signed and dated, and submitted to the IRB;
- ICF(s) contain all required elements and information;
- Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- There are adequate provisions to protect the privacy of subjects and to maintain the privacy and confidentiality of data;
- Instruction and/or informational sheet(s) are available to be given to the research subjects, as appropriate;
Appropriate safeguards have been included to protect vulnerable subject populations.

At IRB meetings each protocol shall be reviewed and discussed with any controverted issues, and their resolution, recorded. The motion for action will typically be made by the primary reviewer, may be amended as necessary, and will be seconded by another voting member. The potential actions of the IRB are delineated in other sections of this Operations Manual. All IRB actions will be documented in correspondence sent to the PI and verified by the signature of the IRB Chair, a Vice-Chair, or designee.

The IRB will decide upon one of the following actions by a majority vote of the members present:

- Approval
  - Approved as submitted, no stipulations
  - Approved with not substantive changes
  - Approved with substantive changes
- Deferral
- Disapproval
- Tabled
- Withdrawal

### 4.2.8.1 Approval

The IRB approves the protocol, ICF(s), and other study documentation as submitted (i.e., without stipulation).

A Notice of IRB Approval, signed by the IRB Chair, a Vice-Chair, or designee, validated ICF(s), and other documents requiring validation (e.g., subject diaries, advertisements) will be provided to the PI. The PI may only begin advertisement, recruitment, screening, and enrollment upon receipt of the Notice of IRB Approval and the finalization of any contract (i.e., Grants and Contracts).

It is the responsibility of the PI to forward a copy of the final protocol and validated materials to the applicable facility, sponsor, and/or funding agency, as required.

All ICFs validated by the IRB will have two (2) dates; the “Approved” date, which is the date of IRB approval, and the “Valid Until” date. The valid until date is the date set by the IRB for completion of continuing review. The interval for the approval of any item presented to a convened IRB will be for 1 year, unless otherwise specified by the IRB.

The approval of the convened IRB will be binding except that the Institution/Institutional Official may always disapprove a study that has been approved by the IRB. However, the converse is never true.

### 4.2.8.2 Review with Stipulations

The IRB may confer its approval contingent upon clarifications and/or revisions that are specifically detailed in a Notice of IRB Comments that is signed by the IRB Chair, a Vice-Chair, or designee. No
research activities, including advertisement, recruitment, screening, or enrollment, may begin until all requisite stipulations have been satisfactorily addressed.

At the convened IRB meeting, an assessment will be made whether the modifications/clarifications are substantive or not substantive in nature.

If the IRB determines that the modifications/clarifications are substantive, that finding will be documented in the minutes, and PI’s responses and corresponding revised documents will be presented to the same IRB committee at a subsequent convened IRB meeting to assess whether the modifications/clarifications are sufficient. Upon re-presentation to the convened IRB, the IRB will focus only on those issues that were deemed to be substantive in nature. At the time of initial review a vote will be taken and at the subsequent convened IRB meeting the IRB will consider only those changes identified as substantive in nature. The IRB’s vote at the re-presentation will focus only on those issues presented.

If it is determined by the convened IRB that the stipulations/clarifications are not substantive in nature, that finding will be documented in the minutes, and the PI’s responses and corresponding revised documents may be reviewed and verified via expedited review in the IRB office, provided the stipulations do not require deliberation by the convened IRB. The IRB Chair, a Vice-Chair, or designee may, at his/her discretion, opt to refer the PI’s responses, etc., to the convened IRB for consideration.

The PI’s response should include a cover letter, responding point by point to each stipulation. The responses should summarize the changes made, and note which sections of the protocol, ICF, or supporting documents were changed in response. Tracked and untracked documents should be submitted. The tracked document should include only changes since the last submitted version. Changes should be tracked with the Microsoft Word track changes or similar program that clearly delineates insertions and deletions. Investigators are discouraged from submitting separate amendments before resolving original stipulations.

Upon receipt of the PI’s response to the IRB stipulations/request for clarification, an IRB staff member may conduct a pre-review of the submitted documents prior to review by the Chair, a Vice-Chair, or designee.

A letter signed by the PI addressing the stipulations/clarifications should accompany any revised documents. All documents should have a version date or number for ease of identification and document control.

Approval is conferred following the verification that all IRB stipulations have been satisfactorily addressed. The Notice of IRB Approval, signed by the IRB Chair, Vice-Chair, or designee, validated study material(s) will be provided to the PI for use. On a monthly basis the members of the IRB will be notified of all items reviewed and approved via expedited review in the preceding month (Notification to IRB of Documents Reviewed/Approved via Expedited Review Procedures document). Advertisement, recruitment, screening, and enrollment in a study may only begin upon receipt of the Notice of IRB Approval and the finalization of any contracts.

It is the responsibility of the PI to forward, as required, a copy of the final protocol and validated materials to any applicable facility, sponsor, and/or funding agency.

All ICFs validated by the IRB will have two (2) dates; the “Approved” date, which is the date of IRB approval, and the “Valid Until” date. The valid until date is the date set by the IRB for completion of continuing review. The “Approved” date (approved/anniversary date) will be the date that all stipulations have been addressed and resolved. Continuing review must occur within one year of that date, unless
otherwise stipulated, and must occur at least once a year. The institutions follow federal guidance\(^\text{12}\) regarding fixed anniversary dates.

The approval of the convened IRB will be binding except that the Institution/Institutional Official may always disapprove a study that has been approved by the IRB. However, the converse is never true.

The interval for the approval of any item presented to a convened IRB will be for 1 year, unless otherwise specified by the IRB.

### 4.2.8.3 Deferral

If the primary reviewer and/or the IRB determine that the information provided by the PI is not sufficient to complete a thorough review and render a determination\(^\text{13}\), the study will be deferred. The reasons for deferral may include that the PI needs to clarify specific substantive issues, submit missing, or significantly revised, materials, and/or attend a meeting to promote discussion and understanding of an aspect(s) of the research. The IRB does not vote on a motion to defer a study. The final decision to defer a study is made by the meeting Chair, usually based on the recommendation of the primary reviewer and with the general consensus of the members present.

The reason(s) for deferral will be recorded in the IRB meeting minutes.

If a research protocol is deferred a *Notice of IRB Deferral* signed by the IRB Chair, a Vice-Chair, or designee, will be provided to the PI, documenting the reason(s) for deferral and specifying the additional information or revisions required for re-presentation. Upon receipt of the requested information and/or revised documents, the Chair, a Vice-Chair, or designee may first review the application. If deemed acceptable to proceed, the PI’s response, including attendant documents, will be scheduled for the next convened meeting of the IRB that initiated the deferral.

### 4.2.8.4 Disapproval

The IRB shall disapprove any research that it determines to be unethical in nature. A *Notice of IRB Disapproval* letter, signed by the Chair, a Vice-Chair, or designee, will include a statement of the reasons for disapproval and give the investigator an opportunity to respond in writing for reconsideration at a subsequent convened meeting of the IRB that initiated the deferral. The reason(s) for disapproval will be recorded in the IRB meeting minutes.

If a PI wishes to request the IRB’s reconsideration, s/he may ask for formal reconsideration, as described in elsewhere in this document, *Request for Reconsideration*.

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\(^{12}\) Office for Human Research Protections Guidance on IRB Continuing Review of Research, 10 November 2010 and IRB Continuing Review after Clinical Investigation Approval, February 2012

\(^{13}\) OHRP recommends that research be deferred if they require, “…substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the [IRB] determinations…” excerpt from OHRP Guidance on Written IRB Procedures, July 01, 2011
4.2.8.5 Tabled

This motion is to enable the IRB to set aside a pending question in such a way that its consideration may be resumed at the will of the IRB.

In the event that an IRB deliberation and vote is tabled, the IRB may establish a subcommittee or seek the guidance of a consultant or expert. This expert could be a fellow IRB member with the required expertise, a member of the Tufts MC /TUHS community, or an outside consultant (see section Utilization of Outside Expertise of this document). Additionally, the IRB may choose to invite the PI to the next convened meeting for discussion and clarification.

4.2.8.6 Withdrawal

In the event that an application must be withdrawn from a meeting agenda without prejudice, the PI, the IRB Chair, a Vice-Chair, or designee, or the primary reviewer may withdraw a research application from a scheduled IRB review. A withdrawal may only be initiated before a study is presented at a convened IRB meeting. If a study is withdrawn, it may subsequently be forwarded to either IRB for review. Reasons for withdrawal include a primary reviewer being unable to attend the meeting, new information learned too soon before the IRB meeting that members have not had sufficient time to review, in the determination of the primary reviewer or Chair there are too many material issues to which the PI has not responded prior to the meeting.

4.2.9 Responses to IRB Reviews

Responses to IRB review comments/stipulations should be completed within three (3) months; otherwise, a new submission may be required, as determined by the IRB Chair, a Vice-Chair, or designee. This applies to new research proposals and research presented for continuing review. Provisions will be made for extending the three (3) month response time, in the event that the PI justifies extenuating circumstances to the satisfaction of the IRB Chair, a Vice-Chair, or designee. The IRB Chair, a Vice-Chair, or designee will review such considerations on a case-by-case basis and render a decision.

If substantial stipulations potentially affecting subject safety are addressed at the time a modification to a previously approved study or a continuing review is reviewed by the convened IRB, the IRB may require a shorter response time. If so, this will be communicated in writing to the PI and will be documented in the minutes. Failure to respond to such review comment stipulations within the designated response time may result in the IRB stopping study activities.

In the normal course of review of the PI’s response(s) to initial review the IRB Coordinator may conduct a preliminary review of responses and present his/her findings to the Chair, a Vice-Chair or designee. The IRB Chair, a Vice-Chair, or the designee, will then review the submitted revisions to verify that they comply with the stipulations determined by the convened IRB. If the reviewing IRB Chair, Vice-Chair, or designee deems the responses satisfactory, a Notice of IRB Approval will be forwarded to the PI (see above) or forwarded to the last reviewing IRB for reconsideration.

If the PI’s response(s) are not deemed satisfactory, the remaining requested revisions, clarifications, etc., will be documented in the study file, and will be communicated to the PI/research team either in writing or orally. Communication with the PI/research team will be documented in the study file.
Additionally, certain issues may dictate that an IRB Vice-Chair or designee specifically forward a PI’s response to IRB stipulations to the IRB Chair for review. At his/her discretion the reviewing Chair, Vice-Chair, or designee, may return the PI’s response to IRB stipulations to the last reviewing IRB for review.

4.2.10 Request for Reconsideration

A PI may request, in writing, the IRB reconsider a decision made by the convened IRB concerning a research protocol. Typically the original primary reviewer will present the requested reconsideration at a convened meeting of the IRB that initiated the action(s). If the original primary reviewer is not available, the IRB Chair may either defer reconsideration until the original primary reviewer is available, or appoint a different IRB member to present the reconsideration or may opt to present the reconsideration him/herself. Request for reconsideration may involve stipulations for approval, as well as voted actions (e.g., disapproval). The decision of the convened IRB will be documented in the minutes and will be final; the decision will be forwarded to the PI in writing.

4.2.11 Establishment of a Subcommittee

In the event of a tabled IRB deliberation and vote, or a deferral, or a request for reconsideration, or another reason deemed necessary by the convened IRB or Chair, the IRB may establish a subcommittee to discuss the protocol with the PI.

The Chair will appoint persons to the subcommittee, and will specifically appoint a subcommittee Chair. Typically, a subcommittee will be composed of IRB members. However, persons at the institutions who are not IRB members, or experts and consultants outside of the institutions, may be asked to meet with the subcommittee to discuss the research. The PI may also be invited to meet with the subcommittee or the convened IRB to address specific issues raised by the IRB. The results of any subcommittee review, including recommendations, shall be reported to the convened IRB when the issues are satisfactorily addressed.

The convened IRB will discuss the recommendations of the subcommittee and review any new materials that have been submitted. The convened IRB may accept or reject the recommendation of the subcommittee. The decision of the convened IRB will be final except that the Institution/Institutional Official may always disapprove a study that has been approved by the IRB; however, the converse is never true. The PI will be informed in writing of the final decision.

4.3 Continuing Review

In accordance with 45 CFR 46.109(e) and 21 CFR 56.108(a)(1) and 56.109(f), the IRB will conduct continuing review of previously approved research at intervals appropriate to the degree of risk, but not less often than once per year (i.e., on or before the anniversary of the previous IRB review). Note: For the purposes of this manual the term “continuing review” is used as opposed to “progress report,” which is also used in federal regulation and guidance.

14 FDA: Continuing Review After Study Approval – Information Sheet Guidance for IRBs and Clinical Investigators
15 OHRP: Guidance on Continuing Review
The IRB will determine the frequency of continuing review at each continuing review. Depending upon the level of risk or other pertinent factors, such as the participation of vulnerable populations, the safety plan, the presence of a DSMB, etc., the IRB has the discretion to require continuing review on a more frequent basis. The IRB may, for example, require the PI to submit a progress report after enrollment of each subject, or prior to increasing dosage of a particular drug, or semi-annual review, etc. The IRB minutes will specify the frequency of review, as will the letter to the PI.

For protocols that are scheduled for continuing review, the IRB may send a courtesy reminder to the PI 2 months prior to expiration of IRB approval. Should a response not be received to the initial courtesy reminder, a second notice courtesy reminder may be sent by the IRB. Regardless of the courtesy reminder, it will be the PI’s responsibility to ensure that the continuing review materials are submitted in sufficient time to allow review by the convened IRB or by expedited review, as appropriate, prior to IRB approval expiration. To help aid in maintaining fixed anniversary dates (see below) and to allow sufficient processing time, continuing review applications should not be submitted more than 60 days prior to expiration. Applications submitted more than 60 days prior to expiration may require the submission of updated information before a study can undergo continuing review.

Failure of the PI to submit the continuing review application per the dates outlined by the IRB in the courtesy reminder(s) may result in delay of IRB review of the research and may cause the IRB approval to lapse. In the event that the IRB approval lapses, no research-related activity may take place. The PI may request in writing special consideration from the IRB Chair to continue to follow a research subject(s) in the event approval lapses (e.g., subject’s safety would be compromised by a lapse in research-related activity). The IRB Chair will consider such requests on a case-by-case basis. Any such limited permission will be documented in the IRB study file and will be conveyed to the PI in writing. The convened IRB will be notified if the Chair exercises this rare dispensation. In such a case, the PI will be required to expeditiously prepare and submit the requisite continuing review materials.

Continuing review must be substantive and meaningful. The IRB will apply the same criteria for approval of continuing review as it does in the initial review (i.e., acceptable risks, potential benefits, informed consent, safeguards for subjects). The same rules apply to continuing review as described previously for initial review. The concentration of the review may change within the approval year (i.e., new federal regulation or new federal or institutional guidelines or new study-specific information learned since the last IRB review); therefore, it is possible that revisions, enhancements, and/or clarifications of the study will be required at continuing review.

The IRB maintains fixed anniversary dates for continuing review as permitted by OHRP and FDA guidance. For studies that undergo continuing review within thirty (30) days before the IRB approval period expires, the IRB will retain the anniversary of the expiration date from the initial IRB approval as the expiration date of each subsequent one-year approval period. This will be true if approval is conditional (i.e., stipulations) or not.

If IRB approval of an ongoing study lapses (i.e., IRB review did not occur) and the IRB subsequently reapproves the study, the IRB will re-approve the study for a period of less than 1 year so as to retain the

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original anniversary date on which prior approval periods expired. The fixed anniversary date will be preserved; a new anniversary date will not be established.

When a study is reviewed within 30 days before IRB approval expires and stipulations exist, the PI should reply by the fixed anniversary date and all stipulations should be resolved by that date.

4.3.1 Exempt Research and Continuing Review

Research that is granted an exemption at the time of initial review will not be required to undergo continuing review; the exempt status of the research will not expire. When an exemption is granted, the PI will be advised in writing of the need to obtain IRB approval prior to initiating a change in the project. Any change a PI proposes to make to a project that has been granted exemption is to be submitted to the IRB in writing. The Chair, a Vice-Chair, or designee will review the requested change and either confirm the exemption still applies or will consider the study for other appropriate review (e.g., not human subject research, expedited review, convened IRB review). The PI will also be instructed to notify the IRB office in writing when the research is terminated.

4.3.2 Expedited Continuing Review

In accordance with federal regulations 45 CFR 46.110 and 21 CFR 56.110, some research may be reviewed and approved via expedited review procedures at the time of continuing review. Expedited review procedures may be used when the protocol is in accordance with federal guidance regarding expedited continuing review. A decision to utilize expedited review procedures will be made by the IRB Chair, a Vice-Chair, or designee. Utilization of expedited review procedures allows for the IRB Chair, a Vice-Chair, or designee, to exercise the authority of the convened IRB, therefore not requiring the research to be presented at a convened meeting of the IRB. However, the IRB Chair, Vice-Chair, or designee, may not utilize expedited review procedures to disapprove a study; such an action can only be taken by the convened IRB. The person who conducts the expedited review should document the permissible category for the approval and it should be documented in the Notice of IRB Approval – Continuing Review.

Research that is reviewed by expedited review is evaluated in terms of the same regulatory criteria as research that is evaluated by a convened IRB. The difference between expedited review and convened IRB review is the number of IRB members who participate in the review.

As a general rule, research that did not qualify for expedited review at the time of initial review will not qualify for expedited review at the time of continuing review, except in limited circumstances as defined by the federal regulations and guidance. It is also possible that research that previously qualified for

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18 Categories of Research that May be Reviewed by an Institutional Review Board through an Expedited Review; Source: 63 FR 60364-60367, November 9, 1998.


expedited review has changed, such that expedited IRB review would not be permitted at the time of continuing review.

### 4.3.3 Convened IRB Continuing Review

If a study was not granted exemption, and was not eligible for expedited continuing review, it will be presented to a convened IRB for review, as required. During continuing review, the IRB will review the current protocol, the ICF(s) that has been used to enroll subjects over the past year, and any proposed changes to the protocol and/or ICF to ensure accuracy and regulatory compliance. At time of convened IRB continuing review, the convened IRB may make the determination that future continuing reviews may be performed by expedited procedures when the remaining research activities present only minimal risk and the criteria for expedited review are met.

Protocols for continuing review are reviewed and presented by a single reviewer. The reviewer of the continuing review will make a motion, another voting member of the IRB will second it, and the convened IRB will vote. The vote must be approved by a majority of members present constituting a quorum. All of the actions referenced in section *Actions by the IRB at Initial Review* may also be taken by the IRB for continuing review and follow parallel procedures as noted below.

As part of continuing review, the Institution(s) has the authority to appoint one (1) or more individuals (other than the researcher) to observe the consent process or the research and to report to the IRB with any findings. The IRB shall appoint such an individual whenever the IRB determines (based on information available such as serious adverse event reports, deficiencies noted in the IRB files, media or scholarly reports of research activity) that monitoring is in the best interests of the research subjects.

### 4.3.4 Quorum of the Membership

As described elsewhere in this manual.

### 4.3.5 Deliberation and Voting Procedure

As described elsewhere in this manual.

### 4.3.6 Preliminary Review

As described elsewhere in this manual.

### 4.3.7 Primary Review

As described elsewhere in this manual.

### 4.3.8 Secondary Review

The use of a secondary reviewer is not required for continuing review; however, it may be used on an as needed basis, as determined by the IRB Chair, a Vice-Chair, or designee.
4.3.9 Actions Taken by the IRB at Continuing Review

As described elsewhere in this manual.

4.3.10 Responses to IRB Continuing Review

As described elsewhere in this manual.

4.3.11 Request for Reconsideration

As described elsewhere in this manual.

4.3.12 Establishment of a Subcommittee

As described elsewhere in this manual.

4.4 Review of Modifications during Approval Period

For the purpose of this operations manual, modification, amendment, addendum, revision, and change may be used interchangeably.

The IRB must approve any change in a protocol prior to the research team’s initiation of that change, even if the change reduces risk. Such changes may be reviewed and approved by expedited review or may require review and approval by the convened IRB.

A change in protocol may be as simple as a new recruitment advertisement, or as complex as the addition of an additional study arm or a new subject population. The only exception to the requirement of obtaining IRB approval prior to initiating a change in protocol is when a change is urgently necessary to eliminate apparent immediate hazards to a subject(s). Under such circumstances, the Principal Investigator is to contact the IRB Chair, or the IRB office, immediately.

4.4.1 Expedited Review during the Approval Period

Whether a change may be reviewed and approved via expedited review or requires review by the convened IRB will be predicated on whether the change is minor and involves minimal risk or greater than minimal risk, as defined by federal regulations/guidance. In accordance with federal regulation 21 CFR 56.110 and guidance, changes in previously approved research during the approval period may be reviewed and approved by expedited review procedures. Only those changes that constitute minimal risk may be reviewed and approved via expedited review. Changes must not involve greater than minimal risk or result in a decrease in benefits to qualify for expedited review. The IRB Chair, a Vice-Chair, or designee will be responsible for reviewing such changes.

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21 45 CFR 46.110; 21 CFR 56.110

for determining whether or not the change is minimal risk or greater than minimal risk. In the event of a question, the IRB Chair will make any final decision regarding the assessment of risk.

Examples of minor changes in previously approved research which may be approved via an expedited review procedure in accordance with regulations at 45 CFR 46.110(b)(2) and 21 CFR 56.110(b) by the IRB generally include:

- Administrative changes
- Changes falling into standard categories for expedited approval
- Changes improving risk:benefit profile (e.g., eliminating blood collection for research purposes that is not performed for subject safety).
- Minor changes in requested enrollment numbers
- Change in risks in response to serious adverse event reports or changes in an Investigator’s Brochure.

The IRB Chair, Vice-Chair, or designee may opt to forward a request for change to the convened IRB even if it qualifies for expedited review.

4.4.1.1 Form(s) and Process for Expedited Review during the Approval Period

If the PI wishes to change a research protocol or any research document during the course of the study, the proposed change(s) are to be submitted in writing to the IRB for consideration. It is the responsibility of the PI to identify the changes made in the research documents (e.g. highlighted or tracked documents). A letter signed by the PI summarizing the proposed changes should accompany any proposed changes/revised study documents. All documents should have a version date or number for ease of identification and document control.

There are no specific forms to request a change in protocol unless the change(s) modify information previously submitted on a Form II, III, VI, or VI. If a revised IRB form is indicated, it should include the signature of the PI and any requisite attachments.

Upon receipt of the PI’s request to change the study, an IRB staff member may conduct a pre-review of the submitted documents prior to them being forwarded to the IRB Chair, a Vice-Chair, or designee for expedited review. Upon review, the IRB Chair, a Vice-Chair, or designee, may determine that the revisions present greater than minimal risk and/or should be reviewed at a convened IRB meeting. In granting expedited approval, the reviewer should document the basis for the approval and any relevant findings.

If modification/clarification of the proposed change is required before expedited review and approval may be granted, the reviewer or an IRB staff member will communicate the requested modification/clarification to the PI or a research team member. The communication may be in writing or oral. The information communicated to the PI or a research team member will be documented in the study file.

Approval is conferred via the Notice of Approval -- Expedited Review Procedure and is signed by the reviewing Chair, Vice-Chair, or designee; validated study material(s) will be provided to the PI, as applicable. On a monthly basis the members of the IRB will be notified of all items reviewed and
approved via expedited review in the preceding month (*Notification to IRB of Documents Reviewed/Approved via Expedited Review Procedures* document).

It is the responsibility of the PI, as necessary, to forward a copy of the final protocol and validated materials to the applicable facility, sponsor, and/or funding agency.

All ICFs validated by the IRB will have two (2) dates; the “Approved” date, which is the date of IRB approval, and the “Valid Until” date. The valid until date is the date set by the IRB for completion of continuing review.

The approval will be final except that the Institution/Institutional Official may always disapprove a change to a study that has been approved by the IRB; however, the converse is never true.

### 4.4.2 Convened IRB Review during the Approval Period

In accordance with 45 CFR 46.110 and 21 CFR 56.110, minor changes in previously approved research during the approval period may be reviewed and approved using expedited review procedures if the change(s) are minimal risk and do not increase risks or decrease benefits. In the event that a change(s) adversely affects the risk: benefit ratio, or is greater than minimal risk, or is deemed to have an apparent effect on the risk: benefit ratio by the IRB Chair, a Vice-Chair, or designee, the proposed change will be forwarded the convened IRB for review. A single primary reviewer will usually present changes. At the discretion of the IRB Chair or designee a secondary reviewer may be appointed.

### 4.4.3 Quorum of the Membership

As described elsewhere in this manual.

### 4.4.4 Deliberation and Voting Procedures

As described elsewhere in this manual.

### 4.4.5 Preliminary Review

As described elsewhere in this manual.

### 4.4.6 Primary Review

As described elsewhere in this manual.

### 4.4.7 Secondary Review (if deemed necessary)

As described elsewhere in this manual.
4.4.8 Action by the IRB at Full Board Review During the Approval Period

As described elsewhere in this manual.

4.4.9 Responses to IRB Review

As described elsewhere in this manual.

4.4.10 Request for Reconsideration

As described elsewhere in this manual.

4.4.11 Involuntary Suspension/Termination of Research Protocols and Suspension/Termination Reporting

The IRB has the authority to suspend or terminate its approval of a study. When practical, such action will be taken by vote of the members at a convened IRB meeting. In the case of an emergency, in order to protect the safety of the study subject(s) the IRB Chair or a Vice-Chair may suspend enrollment and/or any portion of a study without waiting for a convened meeting of the IRB; however, the Chair or a Vice-Chair may not terminate the study. In such cases, the IRB Chair (or Vice-Chair, as appropriate) will notify the IRB members of the suspension at the next regularly scheduled meetings of the IRB.

A suspension/termination may be appropriate for any of the following reasons:

- Unexpected death or serious harm to a study subject.
- Unanticipated problems involving serious harm or risk of serious harm to a study subject, such as known or suspected contamination of a study drug.
- Failure of the PI to provide information requested by the IRB.
- Known or potential non-compliance of the PI and/or a research team member with human subject regulations or the requirements or determinations of the IRB.
- Other circumstances that, in the judgment of the IRB, the IRB Chair, or a Vice-Chair necessitate suspension/termination to protect study subjects from harm.

In all cases, in a timely manner the IRB Chair or Vice-Chair will inform the PI in writing of the suspension/termination. The letter to the PI must state the reason for the suspension/termination. In cases of immediate, significant risk to human subjects, the IRB Chair or designee may communicate the suspension/termination orally while written materials are prepared.

In the case of a suspension, the letter is to specify whether the suspension applies only to the enrollment of new subjects, or also requires the cessation of all study procedures on subjects who have already been enrolled.

In the case of a termination, no new subjects may be enrolled and all study activities involving enrolled subjects must cease. Exceptions may be made by the Chair or Vice-Chair in circumstances where subjects are receiving intervention that cannot be discontinued for safety reasons. These potential instances will be reviewed on a case-by-case basis.
The IRB Chair or Vice-Chair will immediately notify the Institutional Officials and the Manager of IRB Operations of the suspension or termination.

As necessary, the Institutional Official will immediately notify OHRP, FDA, and other appropriate agencies, as required, of the suspension or termination via telephone and initiate an investigation. Following the telephone call, the Institutional Official will send without delay a written confirmation to OHRP, FDA, and other appropriate agencies, as required regarding the initial action taken. Subject to further investigation, a final report or follow-up status letters will be issued to OHRP, FDA, and other appropriate agencies, as required. The initial letter to OHRP, FDA, and other appropriate agencies, as required will specify the action taken by the IRB and the reason for that action, and may contain any additional information that the Institutional Official deems necessary. In the case of a funded study, the Institutional Official will also provide notice to the funding agency and, in the case of a study of a drug or device within the jurisdiction of the FDA, to the FDA.

Depending on the particular circumstances and timing the convened IRB may be involved in this process. Otherwise, the IRB Chair, or a Vice-Chair, will inform members of the IRB at the next convened meetings of the notification(s) of the suspension/termination provided by the Institutional Official to OHRP, FDA, and other appropriate agencies.

Given the particular circumstances of each case, with input from the IRB Chair and the Manager of IRB Operations, the Institutional Official will determine whether or not study subjects should be notified of the suspension/termination. If a decision is made to notify study subjects, the IRB Chair, the Institutional Official, and the Manager of IRB Operations, in consultation with the PI, will determine the content of the notice. The members of the IRB will be informed of any notice given to study subjects.

In all cases in which a study has been suspended, study activities cannot resume until the members of the last reviewing IRB have scrutinized the circumstances of the suspension and voted at a convened IRB meeting to permit reactivation of the study. The IRB may vote to reopen the study – with or without modification, continue the suspension pending further investigation, or terminate the study. If the PI wishes to resume study activities of a study that has been terminated, the PI is to submit a modified new study application for review by the IRB.

None of the above provisions apply to circumstances in which the PI does not make a timely submission of the materials required for continuing review. In such circumstances, the provisions of Section 4.3 — Continuing Review are applicable.

Information regarding all suspensions/terminations will be presented at the next scheduled IRB Executive Committee meeting.

### 4.4.12 Protocol Reactivation

A PI may request reactivation of a study s/he previously terminated. To reactivate a terminated study for the purposes of data analysis only, the PI should submit a signed written request to the IRB office, including the required continuing review materials. As needed, the IRB office staff will have any necessary archived materials recalled from off-site storage. Reactivation of studies for the purposes of data analysis only may be reviewed via expedited review procedures; however, the IRB Chair, Vice-Chair, or designee may opt to forward any request for reactivation to the convened IRB.

In the event a PI requests to reactivate a research study for the purposes of additional subject enrollment or other subject intervention activity, the PI should submit a signed written request to the IRB office, including the required continuing review materials. Reactivation of studies for the purposes of additional
subject enrollment, etc., will be reviewed by the same procedures as the initial review (e.g., expedited or convened IRB), provided that the study risk:benefit ratio has not been changed.

In the event that a study is terminated by a PI in error, the PI may reactive the research. To do so, the PI is to submit signed documentation to the IRB office explaining the circumstances under which the study was terminated and the required continuing review materials. As described elsewhere in this manual, the study may be reactivated via expedited review procedures; however, the IRB Chair, Vice-Chair, or designee may forward any request for reactivation to the convened IRB.

A PI may also reactivate an expired research study (i.e., after IRB approval lapsed) by submitting the required continuing review materials. A study whose IRB approval lapses is not considered suspended or terminated by the IRB.

In all cases in which IRB approval of a research study has lapsed, no research-related activities may take place, and may not resume, until the IRB has reviewed and re-approved the study.

### 4.5 Emergency Exemption from Prospective IRB Approval for Use of an Investigational Drug or Biologic\(^{23}\)

An investigator is advised to immediately contact the IRB office if s/he is seeking a one-time emergency use of an investigational drug or biologic (a “test article”). The IRB office will guide the investigator and will contact the IRB Chair, a Vice-Chair, or designee to review the request. The IRB Chair, a Vice-Chair, or designee may also be available by pager if the circumstance occurs outside of normal business hours.

The emergency use of an unapproved investigational drug or biologic requires an IND number. If the individual does not meet the criteria to enroll in an approved IRB study, or if an approved study protocol does not exist at the institution, the usual procedure is for the responsible clinician to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND. In such a case, the IRB prefers written acknowledgment from the sponsor supplying the investigational drug or biologic be on file acknowledging the emergency use and noting agreement of the use of the investigational drug or biologic with the individual in question. The IRB recommends that documentation sent to, and provided by, the IRB be sent to the manufacturer by the PI, as well.

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

As per the FDA, an investigator may request a one-time emergency use of a test article without prior review and approval from a duly constituted IRB.

If a clinician/investigator anticipates additional situations in which the test article might be used, a complete IRB application must be submitted to the IRB for review by the convened IRB as described elsewhere in this manual.

\(^{23}\) *FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Emergency Use of an Investigational Drug or Biologic – Information Sheet*
Emergency use is defined by the FDA as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].

The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB for a single patient use of a drug or biologic considered investigational. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for 1 emergency use of a test article without prospective IRB review.

In order to qualify for emergency use, each of the following conditions must exist:

1. The individual is in a life-threatening situation that needs immediate treatment;
2. No standard acceptable treatment is available; and
3. Because of the immediate need to use the drug, biologic or device, there is not sufficient time to obtain convened IRB approval.

FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. However, in accordance with FDA guidance, it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Per FDA guidance, life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

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

Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

The IRB must be notified in writing by the investigator within five (5) business days of such use. The institutions prefer that the IRB be notified prior to such use. This notification should not be construed as an IRB approval. FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, per FDA regulations, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized.

An IRB must convene and approve the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene the IRB within the time available, the use may proceed without any IRB approval. The IRB will give priority to ensuring that requests are forwarded to the next convened IRB meeting. If the proposed use can safely wait until after the next convened IRB meeting, the clinician must submit an initial review IRB application for review by the convened IRB.

The investigator is to report serious adverse events to the IRB.

The IRB acknowledges that some manufacturers will agree to allow the use of the test article contingent on "an IRB approval letter" before the test article may be shipped. If it is not possible to convene a
meeting of the IRB within the time available, the investigator is to submit to the IRB detailed information about the individual’s condition and the test article. Such documents include a detailed letter addressing the subject’s medical history and current condition, a protocol or other detailed document addressing test article administration, monitoring, etc., detailed test article information (e.g., Investigator’s Brochure), an ICF, and a letter from another clinician not involved in the individual’s care that confirms that standard care options have been exhausted. After review by the IRB Chair, Vice-Chair, or designee a written statement will be sent to the sponsor stating that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). This, however, is not to be construed as an "IRB approval."

4.5.1 Limits on Use of Data Obtained from Emergency Use under FDA Exemption

Regulations (45 CFR 46.103(b) and 46.116(f)) do not permit research activities to be started, even in an emergency, without prior IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject. To be exempt from the requirement for IRB review for the emergency use of a test article in a life threatening situation, an investigator must not use the data in a systematic investigation designed to develop or contribute to generalizable knowledge or else the exemption no longer applies. To comply with this limitation, investigators must follow these three rules:

1. Do not use the emergency use exemption to circumvent the general requirement for prior IRB review;

2. Do not use data from an emergency in a prospective research study; and

3. Do not report data from an emergency use in a retrospective research study, unless granted specific approval by the IRB.

When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity.

4.5.2 The Informed Consent Process in an Emergency Use Situation

24, 25

If the patient’s medical condition is stable, the investigator is to develop an ICF that the individual will be asked to sign. In some circumstance, the sponsor may provide an ICF for use. If time permits, the IRB Chair or a Vice-Chair should first review the ICF. A copy of the signed ICF is to be given to the subject, and a copy of the ICF should be placed in the subject’s medical record. The ICF must explain the investigatory nature of the test article.

If the physician determines that the subject is not capable of understanding the proposed intervention and cannot sign the ICF, a health care proxy, if one was designated, is to be approached to provide permission. Absent a designated health care proxy, the next-of-kin is to be approached for permission. The recognized priority of the next-of-kin relationship is:

24 FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Drugs and Biologics

25 OPRR Reports: Informed Consent Requirements in Emergency Research, October 31, 1996
1. Spouse
2. Adult children
3. Parent
4. Adult siblings

**4.5.3 Exception from Informed Consent Requirement in Emergency Use Situations**

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

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.

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

2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

3. Time is not sufficient to obtain permission from the subject's legally authorized representative.

4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four (4) conditions above apply, the clinical investigator should make the determination and, within five (5) working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within five (5) working days after the use of the test article [21 CFR 50.23(c)].

The IRB Chair or Vice-Chair will review the notification to ensure that the emergency use meets the applicable regulations. The Investigator is advised that if s/he anticipates the need to use the investigational article in additional subjects, prior review and approval by the IRB is required.

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26 FDA Guidance for Institutional Review Boards and Clinical Investigators 1998 Update: Exception from Informed Consent for Studies Conducted in Emergency Settings” Regulatory Language and Excerpts from Preamble
4.5.4 Exception from Informed Consent for Studies Conducted in Emergency Settings

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above.

For this type of research, the IRB would be guided by the information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble,"27 which is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

4.5.5 Emergency IND Number

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

Per current FDA information, as of 25 July 2003, FDA Contacts for Obtaining an Emergency IND:

<table>
<thead>
<tr>
<th>Product</th>
<th>Office/Division to Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug products</td>
<td>Division of Drug Information (HFD-240) 301-827-4570</td>
</tr>
<tr>
<td>Biological blood products</td>
<td>Office of Blood Research and Review (HFM-300) 301-827-3518</td>
</tr>
<tr>
<td>Biological vaccine products</td>
<td>Office of Vaccines Research (HFM-400) 301-827-3070</td>
</tr>
<tr>
<td>On nights and weekends</td>
<td>Office of Crisis Management &amp; Emergency Operations (HFC-160) 301-443-1240</td>
</tr>
</tbody>
</table>

27 Exception from Informed Consent For Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble
4.6 Off-label Use and Investigational Use of Marketed Drugs, Biologics, and Medical Devices

4.6.1 "Off-Label" Use of Marketed Drugs, Biologics and Medical Devices

Good medical practice and the best interests of a patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an IND, IDE or review by the IRB.

4.6.2 Investigational Use of Marketed Drugs, Biologics and Medical Devices

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)].

IRB review is required for studies involving investigational use of marketed drugs, biologics, etc., regardless of whether an IND is required.

When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, per the FDA, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

1. It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2. It is not intended to support a significant change in the advertising for the product;
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

The FDA has provided the following contact information to help determine whether or not an IND or IDE is required in a specific situation:

For DRUG PRODUCTS contact:
Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research

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28 Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices
4.7 Investigational Drugs

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an IND used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

29 FDA Information Sheet Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

30 Treatment Use of Investigational Drugs – Information Sheet
4.7.1 Expanded Access of Investigational Drugs

4.7.1.1 Open Label Protocol or Open Protocol IND

These are usually uncontrolled studies conducted to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. In accordance with FDA guidelines, these studies require prospective IRB review and informed consent. Investigators must complete an application for initial review, which must be approved by the convened IRB as per the procedures outlined elsewhere in this manual.

4.7.1.2 Treatment IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four (4) requirements that must be met before a treatment IND can be issued:

1. The drug is intended to treat a serious or immediately life-threatening disease;
2. There is no satisfactory alternative treatment available;
3. The drug is already under investigation, or trials have been completed; and
4. The trial sponsor is actively pursuing marketing approval.

In accordance with FDA guidance, treatment IND studies require prospective IRB review and informed consent. A sponsor may apply to the FDA for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. The IRB may still opt to review a study even if the FDA has granted a waiver. On a protocol-by-protocol basis the IRB EC will assess whether the IRB review the ICF is needed. If the FDA has not granted a waiver, the investigator must submit an initial review application, which must be reviewed and approved by the convened IRB.

4.7.1.3 Group C Treatment IND

The "Group C" treatment IND was established by agreement between FDA and the NCI. The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial.

Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. Properly trained physicians can generally administer them without the need for specialized supportive care facilities. Group C drugs are distributed only by the NIH under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical study, safety and effectiveness data are collected. Because administration of Group C
drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105].

Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document that must be used if there has been no local IRB review. The IRB EC will decide on a protocol-by-protocol basis the need for the IRB to review use of investigational agents with Group C Treatment INDs.

4.7.1.4 Parallel Track

The Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent. Investigators must submit a complete initial review application, which must be reviewed and approved by the convened IRB.

4.7.1.5 Emergency Use IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23]. The procedures in the sections addressing initial study applications and emergency exemption from IRB approval will be followed, as applicable.

4.8 Medical Devices

The FDA defines a medical device, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy.

Clinical investigations of medical devices must comply with the FDA informed consent and IRB regulations [21 CFR parts 50 and 56, respectively]. Federal requirements governing investigations

31 National Cancer Institute Investigator’s Handbook
32 Information Sheet Guidance of IRBs, clinical Investigators, and Sponsors – Frequently Asked Questions About Medical Devices, January 2006
33 Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors
34 Device Advice: Device Regulation and Guidance
involving medical devices were enacted as part of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990. These amendments to the Federal Food, Drug, and Cosmetic Act define the regulatory framework for medical device development, testing, approval, and marketing.

Except for certain low risk devices, each manufacturer who wishes to introduce a new medical device to the market must submit a pre-market notification to FDA. FDA reviews these notifications to determine if the new device is "substantially equivalent" to a device that was marketed prior to passage of the Amendments (i.e., a "pre-amendments device").

If the new device is deemed substantially equivalent to a pre-amendments device, it may be marketed immediately and is regulated in the same regulatory class as the pre-amendments device to which it is equivalent. (The pre-market notification requirement for new devices and devices that are significant modifications of already marketed devices is set forth in section 510(k) of the Federal Food, Drug, and Cosmetic Act. Devices determined by FDA to be "substantially equivalent" are often referred to as "510(k) devices."

If the new device is deemed not to be substantially equivalent to a pre-amendments device, it must undergo clinical testing and pre-market approval before it can be marketed unless it is reclassified into a lower regulatory class.

### 4.8.1 Investigational Device Exemption (IDE)\(^{35}\)

An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of the IDE regulations [21 CFR part 812].

Certain clinical investigations of devices (e.g., certain studies of lawfully marketed devices) may be exempt from the IDE regulations [21 CFR 812.2(c)].

Unless exempt from the IDE regulations, an investigational device is categorized as either "significant risk" (SR) or "non-significant risk" (NSR) (see section Significant Risk and Non-significant Risk Medical Device Studies).

The study may not commence until FDA has approved the IDE application and the IRB has approved the study.

In contrast, NSR device studies do not require submission of an IDE application to FDA. Instead, the sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)].

Unless otherwise notified by FDA, a NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements. The abbreviated requirements address, among other things, the requirements for IRB approval and informed consent, recordkeeping, labeling, promotion, and study monitoring. NSR studies may commence immediately following IRB approval.

\(^{35}\) 21 CFR 812
4.8.2 IRB Review of the Protocol and Informed Consent

Once the final SR/NSR decision has been rendered by the IRB (or FDA), the IRB must consider whether or not the study should be approved. In considering whether a study should be approved, the IRB should use the same criteria it would use in considering approval of any research involving an FDA regulated product [21 CFR 56.111]. The investigator is to submit a complete application for initial review, as described elsewhere in this manual. This application must include a Form III for each device being studied, a copy of the Investigator's Brochure or equivalent supporting materials, and information necessary for the SR/NSR determination as outlined elsewhere in this manual.

Some NSR studies may also qualify as "minimal risk" studies, and thus may be reviewed through an expedited review procedure [21 CFR 56.110].

FDA considers all SR studies to present more than minimal risk, and thus, full IRB review is necessary. In making its determination on approval, the IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Procedures for initial approval, continuing review, and amendment are otherwise as for other studies.

4.8.3 Significant Risk and Non-significant Risk Medical Device Studies

IDE regulations [21 CFR part 812] describe two (2) types of device studies, significant risk (SR) and non-significant risk (NSR).

A SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

A NSR device investigation is one that does not meet the definition for a significant risk study.

NSR device studies, however, should not be confused with the concept of "minimal risk," a term used to identify certain studies that may be approved through an expedited review procedure.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

SR device studies must follow all the IDE regulations at 21 CFR 812. SR device studies must have an IDE application approved by the FDA before they may proceed. NSR device studies do not have to have an

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36 Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006
4.8.3.1 The NSR/SR Decision

The investigator presents the initial determination to the IRB. This determination may be from the sponsor, or have been previously made by the FDA. The IRB will review the sponsor's SR or NSR determination for an investigational medical device study reviewed. If the FDA has already made a determination, that determination will be final; however the IRB reserves the right to apply protections commensurate with its own assessment of the device and protocol's risk, even if the FDA has determined a device to be NSR.

The investigator must provide the IRB with a description of the device, any reports of prior investigations/studies involving the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The investigator should inform the IRB whether any other IRB(s) has reviewed the proposed study and what determination(s) was made.

For an SR device, or NSR device with an IDE, the convened IRB will make the determination. A NSR device without an IDE may have the determination made by the IRB Chair, Vice-Chair, or designee. When a SR/NSR decision is made by the convened IRB it will be documented in the IRB meeting minutes. When made by the expedited reviewer, the determination will be documented as part of the review.

In making the determination, the IRB will consider the submitted information, the above definition(s), and the prior determination pertaining to similar devices. In deciding if a study poses an SR, the IRB may consider the basis for the risk, including the proposed use of the device, the nature of the harm that may result from use of the device, and any additional procedures and any potential harm they may cause. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB will consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

The IRB may engage outside consultants as necessary, or consult the FDA in making the determination.

The IRB may agree or disagree with a sponsor's initial NSR assessment. If the IRB agrees with a sponsor's initial NSR assessment and approves the study, per FDA, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has

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37 Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies, January 2006

38 Presentation: Institutional Review Board responsibilities in Making the Significant Risk and Non-significant Risk Device Determination

39 Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices, October 26, 2001
been made. The study may be conducted as a SR investigation following FDA approval of an IDE application.

4.8.4 Emergency Use of Unapproved Medical Devices

In accordance with FDA guidance, an unapproved medical device is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Federal Food, Drug, and Cosmetic Act [FD&C Act, 21 U.S.C. 360(e)]. Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices.

An unapproved device may be used in human subjects only if it is approved for clinical testing under an approved application for an IDE under section 520(g) of the FD&C Act [21 U.S.C. 360(j)(g)] and 21 CFR part 812.

The FDA acknowledges that emergencies arise where an unapproved device may offer the only possible life-saving alternative, but an IDE for the device does not exist, or the proposed use is not approved under an existing IDE, or the physician or institution is not approved under the IDE. Using its enforcement discretion, FDA has not objected if a physician chooses to use an unapproved device in such an emergency, provided that the physician later justifies to FDA that an emergency actually existed. The IRB applies the procedures for emergency exemption from IRB approval described for drugs and biologics described elsewhere in this manual to unapproved medical devices.

4.8.4.1 Requirements for Emergency Use of a Device

Each of the following conditions must exist to justify emergency use of a device:

1. The patient is in a life-threatening condition that needs immediate treatment;
2. No generally acceptable alternative for treating the patient is available; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to determine whether these criteria have been met, to assess the potential for benefits from the unapproved use of the device, and to have substantial reason to believe that benefits will exist. The IRB prefers to be notified in advance of such use.

The physician may not conclude that an “emergency” exists in advance of the time when treatment may be needed based solely on the expectation that IDE approval procedures may require more time than is available. Physicians should be aware that the FDA and the IRB expect them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.

40 Guidance for Institutional Review Boards and Clinical Investigators 1998 Update; Medical Devices

41 Emergency Use of Unapproved Medical Devices

42 “Off-label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet Guidance for Institutional Review Boards and Clinical Investigators
In the event that a device is to be used in circumstances meeting the criteria listed above, the device developer should notify the Center for Devices and Radiological Health (CDRH), Program Operation Staff by telephone (301-594-1190) immediately after shipment is made. [Note: an unapproved device may not be shipped in anticipation of an emergency.] Nights and weekends, contact the FDA Office of Emergency Operations (HFA-615) 301-443-1240.

FDA would expect the physician to follow as many subject protection procedures as possible. These include:

- Obtaining an independent assessment by an uninvolved physician;
- Obtaining informed consent from the patient or a legal representative;
- Notifying institutional officials as specified by institutional policies;
- Notifying the IRB; and
- Obtaining authorization from the IDE holder, if an approved IDE for the device exists.

The IRB prefers notification in advance of the use. As for unapproved drugs and devices, the IRB will give priority to ensuring that proposed emergency uses are forwarded to the next convened IRB meeting. If the use can be safely delayed until the convened meeting, the provider should submit the proposed ICF, independent assessment by an uninvolved physician, IDE information, Form III, and other relevant supporting materials to the IRB for review at the convened meeting. If the use must occur prior to the convened meeting, the same materials should be submitted to the IRB office for review by the office staff and IRB Chair, Vice-Chair, or designate. Procedures for review are as presented elsewhere in this manual.

### 4.8.4.2 After-use Procedures

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

- Report to the IRB within five (5) business days [21 CFR 56.104(c)] and otherwise comply with provisions of the IRB regulations [21 CFR part 56];
- Evaluate the likelihood of a similar need for the device occurring again, and if future use is likely, immediately initiate efforts to obtain IRB approval and an approved IDE for the device's subsequent use; and
- If an IDE for the use does exist, notify the sponsor of the emergency use, or if an IDE does not exist, notify FDA of the emergency use (CDRH Program Operation Staff 301-594-1190) and provide FDA with a written summary of the conditions constituting the emergency, subject protection measures, and results.

Subsequent emergency use of the device may not occur unless the physician or another person obtains approval of an IDE for the device and its use. If an IDE application for subsequent use has been filed with FDA and FDA disapproves the IDE application, the device may not be used even if the circumstances constituting an emergency exist. Developers of devices that could be used in emergencies should anticipate the likelihood of emergency use and should obtain an approved IDE for such uses.
4.8.4.3 Limits on Use of Data in Emergency Device Use Situations

As described elsewhere in this manual.

4.8.4.4 ICF Process in Emergency Device Use Situations

As described elsewhere in this manual.

4.8.4.5 Exception from Informed Consent Requirement

As described elsewhere in this manual.

4.8.4.6 Exception from Informed Consent for Planned Emergency Research

As described elsewhere in this manual.

4.8.4.7 Evening/Weekend Emergency Approval for Treatment of a Patient by Use of Investigational Modalities

During evening hours, weekends, or holidays, the IRB Chair or Vice-Chair may be available by pager. An IRB office staff person is also on call and available by pager. If it is determined by the attending physician that the use of investigational therapy must not be delayed until normal business hours, and the IRB Chair or Vice-Chair or IRB office staff persons is not available, the attending physician may proceed with the emergency investigational intervention for the specific patient in accord with FDA regulations.

4.8.5 Humanitarian Use Device (HUD) 43, 44

A HUD is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year. The Office of Orphan Products Development (OOPD) determines if a device meets specific requirements, including scientific rationale and population prevalence, for designation as a HUD.

A Humanitarian Device Exemption (HDE) 45 application is similar to a pre-market approval, but because a HUD is exempt from the effectiveness requirements of a pre-market approval, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. However, the HDE must contain sufficient information for FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the

43 FDA regulations; 21 CFR 814, subpart H, Humanitarian Use Devices


45 Humanitarian Device Exemption Overview
probable risks and benefits of currently available devices or alternative forms of treatment. Section 520(m)(2)(C). An approved HDE authorizes marketing of an HUD.

A HUD should be administered only if such use has been approved by the IRB.

HUDs should not be used until after the HDE applicant obtains approval of the HDE from FDA and the IRB approves its use. The IRB will ensure that HDE approval has been granted before approving the device for use at their institution.

### 4.8.5.1 Initial review of a HDE

Initial IRB approval will be performed at a convened IRB meeting. The IRB does not need to review and approve individual uses of an HUD, but the IRB may approve use of the HUD without any further restrictions, under a protocol, or on a case-by-case basis. The investigator is to submit an initial review application as outlined elsewhere in this manual.

### 4.8.5.2 Continuing review of a HDE

The IRB may approve the use of the device for a period of time, not to exceed 1 year. In some higher risk cases, the IRB may approve a HUD for a specific number of patients and require a summary report before approving the use in additional patients. This will be assessed on a case-by-case basis and will be documented in the IRB meeting minutes.

Continuing review should follow the requirements found at 21 CFR 56, and may be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that convened IRB review should be performed. A finding whether expedited continuing review is acceptable will be made by the convened IRB and documented in the IRB meeting minutes.

### 4.8.5.3 Informed Consent with an HUD

Regulations do not require informed consent for a HUD. Because a HDE provides for marketing approval, use of the HUD does not constitute research or an investigation that would normally require consent from the study subjects.

Our IRB requires prospective informed consent, when feasible. Materials developed by the investigator or previously developed by the HDE holder that incorporates information that may be used to assist a patient in making an informed decision about the use of the device may be submitted. The informed consent process must clearly communicate the potential risks and benefits of the HUD, as well as any procedures associated with the use of the device and alternatives to the use of the device. It must also state that the device is a humanitarian use device for which effectiveness for the labeled indication has not been demonstrated, and explain the nature of HUDs. See 21 CFR 814.104(b)(4)(ii).

Unless it is an emergency, before a HUD is used off-label, the IRB requires following the FDA recommendation that the HDE holder obtain FDA approval of the use following the compassionate use policy for unapproved devices. If the FDA approves the compassionate use request, the physician must

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46 See Chapter III Expanded Access to Unapproved Devices of the IDE Policies and Procedures Guidance Pre-Market Approval
ensure that the patient protection measures are addressed before the device is used and should devise an appropriate schedule for monitoring the patient. If the situation is life threatening and there is not sufficient time to get FDA approval for the off-label use, FDA recommendations in the relevant guidance must be followed and IRB procedures outlined for emergency uses in section 4.6 must be followed.

Sometimes a physician or HDE holder may develop a research protocol designed to collect safety and effectiveness data to support a pre-market approval for the device. In that case, an IDE is not required if the research is within the approved labeling; however, IRB approval for the investigational study must be obtained before the research may begin. Informed consent must also be obtained from the subjects participating in the study. If the research is for a new use, IDE regulations must be followed (21 CFR 812, 50, and 56).

4.9 Unanticipated Problem and Adverse Event Reporting 47, 48

4.9.1 Introduction

This policy discusses the classification and reporting requirements for adverse events and unanticipated problems that occur during the conduct of a research study involving human subjects. Reporting of these types of problems is critical to ensure human subject protections, as these are the types of problems that may require modification to the protocol/ICF. The policy derives from the applicable sections of 45 CFR 46, FDA regulations, including the January 2009 guidance, and the OHRP, including the January 15, 2007 guidance. This policy clarifies the implementation of these regulations and guidance at Tufts MC/TUHS.

4.9.2 Terminology

4.9.2.1 Unanticipated Problem

Definition: An Unanticipated Problem is an incident, experience, or outcome that meets all of the following criteria:

1. The nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the ICF(s).
2. It is related or possibly related to participation in the research.
3. It suggests the research may place the subject or others at a greater risk of harm than was previously recognized.

47 OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse events, January 15, 2007

48 FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs- Improving Human Subject Protections, January 2009
4.9.2.2 Adverse Event (AE)

Definition: An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject’s participation in the research. Every AE is classified as:

I. Non-serious or Serious

II. Related (includes both definite and probable relationships), Possibly Related, or Unrelated to participation in the research.

III. Expected or Unexpected based on the known:
   a. Risks associate with drugs, devices, or other protocol activities described in the IRB approved protocol, supporting documents, and ICFs, or
   b. Natural progression of an underlying illness, or
   c. Health characteristics of the study population.

IV. Internal or External depending on whether the AE occurred at a study site where the Tufts MC/TUHS IRB is the responsible approving body (Internal), or the AE occurred at a research site not under the jurisdiction of the Tufts MC/TUHS IRB (External).
   a. An External AE is most often encountered with multi-center studies where the AE occurred at an outside research site having its own IRB.

4.9.2.3 Serious Adverse Event (SAE)

Definition: A SAE is any AE that:

1. Results in death, or
2. Is life-threatening, or
3. Results in hospitalization or prolongation of existing hospitalization, or
4. Results in a persistent or significant disability/incapacitation, or
5. Results in a congenital anomaly/birth defect, or
6. May jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

4.9.3 Determination of whether an adverse event is an unanticipated problem

An Unanticipated Problem is a major concern of an investigator and the IRB as it generally requires actions such as modification or suspension of the protocol, or informing subjects. All three of the criteria in the definition above must be met to be an Unanticipated Problem. This means that not all Unexpected Serious Adverse Events are Unanticipated Problems since some of them may, for example, not be related to the participation in the research study. Likewise, there does not have to be an AE to be an Unanticipated Problem.

For example, an event may be observed which is unexpected, related to participation in a study, but did not result in harm to the subject. If, however, it is determined that the subject (or others) are at an increased
risk for harm, this would be an Unanticipated Problem. Unanticipated Problems do not only include risks of physical harm, but also psychological, economic, or social harm. Please see the flow chart in Appendix A for more detail, and Appendix B for specific examples.

All Unanticipated Problems must be promptly reported to the IRB. Unanticipated Problems may also require prompt reporting to the appropriate institutional officials, the study sponsor or funding source (if applicable), the FDA (for drug/biologic/device/vaccine, etc., associated events), and/or OHRP.

### 4.9.4 Reporting Requirements and Procedures, and Related Activities

Reports, when required, must be submitted to the IRB for each event occurring for each subject individually using the Tufts MC/TUHS IRB Event Reporting Form. All supporting documentation must be attached to the Event Reporting Form. Reporting requirements and procedures, and related activities are described below and summarized in Table 1. A reporting plan must be included in the protocol, and must be consistent with the requirements below, unless specific modifications were approved by the IRB.

#### 4.9.4.1 Unanticipated Problems

Each Unanticipated Problem requires immediate action by the PI as follows:

1. Immediate corrective action must be taken to eliminate or minimize risk to enrolled subjects. This could necessitate a voluntary hold on further enrollment and/or research activities for already enrolled subjects. If subjects are at immediate risk, these corrective actions must be initiated immediately, and if necessary for subject safety, simultaneous with completion of reporting requirements. In such an instance, the PI should immediately call the IRB office.

2. Enrollment of new subjects should be voluntarily stopped until a revised protocol and/or ICF(s) are reviewed and approved by the Tufts MC/TUHS IRB. In some situations enrollment may continue, provided new subjects are not at risk, and the PI provides the IRB the necessary documentation in support of continuation of enrollment. It may also be necessary for the IRB to formally suspend a study under certain conditions.

3. The problem must be promptly reported to the Tufts MC/TUHS IRB, the study sponsor, and all data monitoring entities involved with the study.
   a. An initial report to the Tufts MC/TUHS IRB must be submitted in writing no later than two (2) business days after the PI/study team become aware of the problem. This report is to briefly summarize the nature of the event, summarize the corrective action plan as developed and initiated at that time, and clarify whether subject enrollment is continuing. In the rare circumstance where an original written report cannot be submitted directly to the IRB office, it may be faxed within 2 business days (617-636-8394). The IRB office may be contacted by phone at 617-636-7512 for necessary guidance, and PIs are encouraged to do so.
   b. An Event Reporting Form must be completed with accompanying documentation addressing each item in this list and submitted to the Tufts MC/TUHS IRB no later than five (5) business days after the PI/study team became aware of the problem.
   c. A report must also be filed with the FDA for studies using investigational drugs and devices, or where the Unanticipated Problem is deemed related or possibly related to an
approved drug or device used in the study. (More information may be obtained at http://www.fda.gov/medwatch/how.htm). Reporting is typically done by the individual or entity to whom the IND or IDE has been issued and is to be in conformity with the agency’s reporting requirements.

Note 1: Like AEs, Unanticipated Problems may be Internal or External, but unlike AEs, BOTH Internal and External Unanticipated Problems must be reported according to the requirements outlined above.

4.9.4.2 Serious Adverse Events (SAE)

Reporting requirements vary for SAEs as follow:

1. A SAE that is Related or Possibly Related and Unexpected meets criteria for an Unanticipated Problem and should be acted upon as outlined above.
   a. This applies to both Internal and External SAEs.
   b. A completed SAE/UP Reporting Form with all necessary supporting documents must be submitted to the Tufts MC/TUHS IRB within five (5) business days of the PI/research team learning of the event.

2. An Internal SAE not meeting criteria for an Unanticipated Problem must be reported to the Tufts MC/TUHS IRB within fifteen (15) business days of the PI/research team learning of the event; the SAE/UP Reporting Form must be used.
   a. If changes are required to the protocol and/or ICF(s), subject enrollment and study activities related to the AE, and not necessary for subject safety, cannot continue until the changes have been reviewed and approved by the Tufts MC/TUHS IRB.

3. An External SAE not meeting criteria of an Unanticipated Problem, but requiring changes to the protocol and/or ICFs must be reported to the Tufts MC/TUHS IRB within fifteen (15) business days of the PI/research team learning of the event. The report is to be made using the SAE/UP Reporting Form.
   a. Subject enrollment and study activities related to the AE, and not necessary for subject safety, cannot continue until the changes have been reviewed and approved by the Tufts MC/TUHS IRB.

4. An External SAE not meeting criteria of an Unanticipated Problem, and not resulting in changes to the protocol and/or ICF(s) are to be summarized and submitted to the Tufts MC/TUHS IRB for review at the time of continuing review, or as required by the IRB approved study protocol.

4.9.4.3 Non-serious Adverse Events

1. All clinically significant Internal Non-serious Adverse Events not meeting criteria of an Unanticipated Problem can be summarized and submitted to the Tufts MC/TUHS IRB at the time of the continuing review, or when the PI terminates the study if this occurs before the date of the next continuing review.

2. All Non-serious External Adverse Events not meeting criteria for an Unanticipated Problem do not need to be reported to the Tufts MC/TUHS IRB.

Table 1. Guidelines for reporting Unanticipated Problems and Adverse Events to the Tufts MC/TUHS IRB.
### Unanticipated Problem: Internal or External

- Immediate reporting as described above
- Completed SAE/UP Reporting Form with supporting documents submitted to IRB within 5 business days

### SAE: Internal or External, Related or Possibly Related, Unexpected

- Meets criteria for an Unanticipated Problem and is to be reported as such

### SAE: Internal, all other situations

- Complete SAE/UP Reporting Form and submit to IRB within 15 business days

### SAE: External, requiring change in protocol or ICFs but NOT considered an Unanticipated Problem.

- Complete SAE/UP Reporting Form and submit to IRB within 15 business days

### SAE: External, all other situations

- Submit a summary using the External SAE Summary Reporting Form all interval events 1) at the time of study Continuing Review, or 2) at the time of study termination if before the next scheduled Continuing Review, or 3) as required by the IRB approved study protocol

### Non-Serious AE: Internal, all situations not considered an Unanticipated Problem

- Using the Summary Reporting Form for clinically significant AEs may be summarized at the time of Continuing Review, or study termination if before the next scheduled Continuing Review

### Non-Serious AE: External, all situations not considered an Unanticipated Problem

- Not required to be reported to the IRB

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### 4.9.5 Responsibilities of the Investigator

All greater than minimal risk protocols are to include a delineation of an action plan for all Unanticipated Problems and Serious Adverse Events (SAEs), including clarification about to whom the events will be reported, such as the IRB, federal agencies, sponsor (if applicable), and the specific reporting timeframes. Statements such as “Adverse events will be reported as per local IRB guidelines” are not adequate. Investigators may propose modifications to these guidelines as appropriate to the protocol; but, the modifications must be approved by the IRB prior to implementation. The PI should propose modifications to the standard reporting plan both in instances where shorter reporting timeframes may be necessary (for example, particularly vulnerable populations or potentially controversial research interventions) or longer (for example, deaths in a minimal risk study in a high risk population where the deaths are likely to be from the underlying disease and not the minimal risk research intervention). If relevant, the plan should also have provision for who will review and submit event reports in the PI’s absence. If the PI cannot modify the main protocol document, the reporting plan is to be outlined in a Site Specific Appendix.

Protocols may contain their own assessment scales for judging the severity of an AE. Typical scales may range from 1 (mild) to 5 (fatal). While these scales may be useful in study analysis, it is important that the PI use the criteria in the Terminology section above to determine if an AE is Serious or Non-Serious for purposes of assessing subject risk and meeting the reporting requirements set forth in this document.

The PI must comply with all reporting requirements noted above. The PI must provide sufficient information to allow the IRB to make an assessment of risk. The IRB may request additional information from the PI. When requested, the PI is expected to provide this additional information within two (2)
business weeks, or sooner if specified by the IRB. If the PI determines that an event is study related or possibly study related, but does not feel that changes to the ICF and/or protocol are necessary, a rationale is to be provided within the timeframe specified by the IRB.

The PI must independently begin initiation of corrective action plans necessary to ensure subject safety while preparing and submitting the required reports.

The PI must provide all reports from DSMBs and other data/safety monitoring committees relevant to the interpretation or follow-up of Unanticipated Problems and Serious Adverse Events. Actions by data/safety monitors to change the conduct of a trial must be reported to the IRB within 7 business days of receipt by the PI. The PI should provide an interim plan for the conduct of the trial while necessary amendments are being prepared. All reports from data/safety monitors must be submitted at time of initial study submission for studies that are ongoing at other sites. All reports obtained after the initial Tufts MC/TUHS IRB approval, or last continuing review, should be submitted at the next scheduled continuing review application.

A summary of all Adverse Events and Unanticipated Problems since the initial protocol approval, or last continuing review, must be submitted with the next scheduled continuing review application. The PI is to assess at that time whether when reviewed in combination, further changes to the protocol and/or ICF may be necessary that were not identified at the time they were individually reported.

4.9.6 Responsibilities of the IRB

The IRB must ensure that research includes adequate provisions for monitoring the data collected to ensure the safety of subjects.

A. The IRB does not conduct the monitoring, but may request, where appropriate, additional monitoring to be performed.
   1. The IRB has the authority to:
      a. Determine the type of data or events that are to be captured under the monitoring provisions.
      b. Request that a data monitor be established for any research.
      c. Request additions or changes to the monitoring entity proposed for the research.
      d. Have a third party observe the research.

B. The IRB may determine:
   1. The timeframes for reporting adverse events and unanticipated problems to the monitoring entity.
   2. The frequency of assessments of data or events captured by the monitoring provisions.
   3. The definition of specific triggers or stopping rules that will dictate when an action is required.
   4. Procedures for communicating to the IRB(s), study sponsor, study investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.

1. The IRB is responsible for reviewing all reported Adverse Events and Unanticipated Problems submitted by the PI.
   a. Sufficient information must be reported to the IRB so that a determination of risk to study subjects can be made.
      i. The IRB has the authority to request changes in the protocol and/or ICF(s) as the result of Adverse Events or Unanticipated Problems
2. The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year.

1. The IRB must review the summary of information provided by the PI of:
   a. Unanticipated Problems
   b. Adverse Events
   c. New findings that may be relevant to the research
   d. Data monitoring reports.

2. The IRB may request changes to the protocol, ICF(s), and data monitoring based on all information available at the time of continuing review. In reviewing the continuing review, the IRB’s focus will be to determine if the information reviewed in combination requires additional changes to the conduct of the study or ICF that was not evident when the events were reported individually.

3. For multi-center studies already ongoing at other sites, the IRB must review a summary of the same information at time of initial review.

3. The IRB may:

   a. Recommend the suspension or termination of a study for investigator non-compliance or unanticipated problems. See institutional Suspension and Termination Policy.

   b. Recommend the reporting by Tufts MC/TUHS Institutional Official to OHRP, FDA, National Institutes of Health (NIH), or other governance or funding agency, study non-compliance or Unanticipated Problems.

4. IRB procedure

   • Preliminary review: Upon receipt of an Event Report in the IRB office, it will be reviewed by the office staff for completeness. Incomplete reports will be returned to the PI for the required missing information. Reports will typically be directed to the Chair, Vice-Chair, or earliest available designated reviewer. For Unanticipated Problems and Events of special concern, the Chair or acting Chair will be contacted and the report brought to his/her immediate attention.

   • Review: Event Reports will be reviewed by an IRB member. This will be done typically by the Chair or Vice-Chair or member designated by the Chair.

   • Upon review of an Event Report, the reviewer will decide if action is necessary to minimize any potential risk(s) to the former, current, and/or future subjects. Actions taken may include:

     o Acknowledge the report, with no changes to the ICF and/or protocol necessary.
     o Request additional information for clarification.
     o Request changes to the ICF and/or protocol in response to the report.
     o Approve accompanying ICF and/or protocol changes submitted by the PI in response to the report, provided the reviewer determines that the modifications constitute “minor changes” as per 45 CFR 46.110.
     o After ensuring that appropriate measures are put in place to ensure subject safety, refer to the next convened IRB meeting any ICF and/or protocol changes that do not qualify as
“minor changes”; a reported event determined to significantly adversely alter the overall risk/benefit profile may be referred to the convened IRB meeting to determine if additional ICF and/or protocol changes are required.

- Subjects may be required to sign a revised or addendum ICF communicating the new information. The new information may also need to be reported to subjects who have completed their participation in the study.
- The research study may be temporarily suspended and/or the research study procedures discontinued/terminated.
- The research study may be suspended or terminated in accord with the institutional “Involuntary Suspension/Termination of Research Protocols and Suspension/Termination Reporting” section of the IRB operations manual.

- The event reviewer will document his/her determination in writing on the Event Report cover sheet. Written documentation, including any communication with the PI regarding the AE, will be kept in the IRB file.

A. Flow chart of reporting categories.
Flow chart showing various relationships between Events (Adverse and Non-Adverse) and Event Reporting categories. Note that “Non-Adverse Events” themselves do not constitute a specific reporting category, but they may include unexpected situations that place subjects at increased risk for harm. If such situations are deemed related, or possibly related to participation in the research study, they would be categorized as Unanticipated Problems.

If the research protocol is suspended or terminated, additional notice shall be provided as discussed elsewhere in this manual.

4.10 Record-keeping Requirements

4.10.1 IRB Record-keeping Requirements

The IRB maintains study-specific records of its activities for at least eight (8) years after completion of the research. The eight (8) year retention policy of the Tufts MC/TUHS IRB is in accordance with, and exceeds, 45 CFR 46.115(b) and the Massachusetts General Laws guiding contract and tort claim \[MGL Chapter 260 §2 and 2A\], respectively.

Under normal circumstances, the IRB defines the completion of the research as the termination of the research protocol by the PI. Termination is defined as all research-related activity has concluded, including subject intervention, follow-up, data queries, etc.

All IRB records (active and terminated) are available for inspection and copying by the FDA, authorized federal or state government agencies, institutional compliance auditors, or hospital accrediting agencies (e.g. JCAHO) in the course of carrying out their respective duties.

The following records are also maintained:

- IRB membership rosters for five (5) years;
- Written policies and procedures, forms and other instructions;
- Minutes of meetings for seven (7) years upon termination of the study.

For each study reviewed by the IRB, a copy of the initial submission (application forms, proposed protocol and informed consent form(s)), together with, but not limited to, the following items as applicable will be retained:

- Notification letters to PI regarding all IRB actions
- Approved protocol(s)
- Approved ICF(s)
- Amendment request(s)
- Serious Adverse Event reports
- Unanticipated event reports
- Continuing Review applications
- HIPAA-related documents
- All SRC comments and responses
- Investigator’s Brochure(s)
PDR excerpts, MSDS Sheets, relevant scientific articles, etc.

- All correspondence received by/sent to the IRB office
- All written information containing materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaire(s), survey instrument(s), advertisement(s), contact letter(s), etc.

The IRB will retain copies of the full agenda provided to IRB members for the meeting for three (3) years.

### 4.10.2 Investigator Record-keeping Requirements

#### 4.10.2.1 Sponsored Research

An investigator will be responsible for maintaining research records as agreed to in clinical trial agreement with a sponsor. The clinical trial agreement should be in accordance with applicable federal and state law regarding record retention.

#### 4.10.2.2 Investigational Drugs

In accordance with 21 CFR 312.57(c) an investigator, or sponsor is to retain the records and reports required by Subpart D of the section for two (2) years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.\(^49\)

#### 4.10.2.3 Investigational Devices

In accordance with 21 CFR 812.140 an investigator, or sponsor, is to maintain the records required by Subpart G of the section during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol.\(^50\)

#### 4.10.2.4 Other

In all other studies that do not have a clinical trial agreement, or are regulated by the FDA, the PI will be required to maintain research records for 7 years after s/he has terminated the study with the IRB.

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\(^{50}\) [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm)
4.11 Accessing the IRB Files

Upon request, a PI and/or research team members will be permitted access to those IRB study files in which they have a participating role. Access will be under the supervision of the IRB office staff. A PI may authorize a study team member to access the IRB study file by providing signed written notification/authorization to the IRB office. It will be the practice of the IRB office to document access to the IRB study file by any member(s) of the research team in the IRB study file. The written authorization from the PI will also be retained in the IRB file.

Members of the Tufts MC Office of Research Administration, and Tufts University Office of the Vice Provost also may access relevant IRB files, as needed, with the permission of the Manager of IRB Operations.

Only materials submitted by the research team may be photocopied by any of the above-cited parties. Official correspondence from the IRB to the PI may also be copied by the above-referenced parties. However, any IRB review(s) or intra-office communications (e.g., Memorandum or Note to File) may not be photocopied without the written and signed authorization of the IRB Chair. IRB meeting minutes may not be copied or accessed by the study team or non-IRB personnel.

An IRB member may access the IRB study file(s) in the course of conducting an assigned review.

All IRB management and staff, including the Institutional Officials, the Chair, the Vice-Chair(s), and the Manager of IRB Operations will have access to all IRB study files. In the event that proceedings, such as those of the Executive Committee or the IRB, require restricted access, the Manager of IRB Operations or his/her designee will maintain such documents.

4.12 Policy on IRB Reviewer Contact with Study Sponsors

During the review of protocols by IRB members, an IRB Reviewer should never directly communicate with a study sponsor; all contact with the study sponsor is to be done by the PI. If an IRB reviewer seeks information from a sponsor, s/he is to discuss the matter with the PI, who may opt to contact the sponsor. The PI may choose to contact the sponsor with the IRB reviewer present (e.g., present and possibly on speakerphone for a conversation); however, this is at the discretion of the PI.

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51 FDA: Sponsor-Investigator-IRB Interrelationship – Information Sheet Guidance for IRBs and Clinical Investigators
5 Special Considerations

This section discusses topics that require special IRB consideration:

- Informed Consent
- Vulnerable Populations
- Women and Minorities in Research
- International Research
- Certificate of Confidentiality
- Definition of Ionizing Radiation
- Subject Complaints

5.0 Informed Consent\textsuperscript{52, 53, 54, 55}

The IRB considers informed consent a dynamic process. There should be an ongoing dialogue between the PI/research team and the (prospective) subject concerning the research; this ongoing dialogue should be throughout the subject’s participation in the research study. The ICF, which formalizes and documents the discussion about the research, must be signed unless the IRB either waives informed consent or written documentation of informed consent. The IRB considers the ICF as documentation of the dialogue that must occur between the PI, or his/her representative, and the prospective subject. The IRB maintains that the ICF, however detailed, is not a substitute for discussion with prospective or enrolled subjects.

The ICF is a statement addressed to the subject that provides information, as required by law, about the study, including but not limited to its procedures, benefits, risks, and alternatives so that the prospective subject may make an informed decision about whether or not to participate in the study. It should be worded in the second person. It should be written at approximately an 8th grade reading level. Technical or medical terms and jargon are to be explained. The ICF may not be coercive or contain exculpatory language; it should be concise, and it should not contain grammatical or spelling errors. The PI/research team is to give the subject or the legally authorized representative adequate opportunity to read it before it is signed.

\textsuperscript{52} FDA: A Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators

\textsuperscript{53} OHRP: Tips on Informed Consent

\textsuperscript{54} OHRP: “Exculpatory Language in Informed Consent,” Cooperative Oncology Group Chairpersons Meeting November 15, 1996

\textsuperscript{55} FDA: IRB Frequently Asked Questions – Information Sheet Guidance for IRBs and Clinical Investigators
Subjects must execute the ICF(s) before participating in the research protocol, unless the IRB grants approval to the investigators to obtain informed consent from the prospective subject’s legally authorized representative or waives the requirements of informed consent.

Informed consent must also be obtained for screening for subject eligibility. If a separate ICF is used for screening, it must also include a brief description of the full study, as necessary for the subject to determine if s/he wants to participate in screening. Investigators may prospectively request waiver or alteration of the consent process for screening; however, waiver will only be granted if the research activities meet the criteria specified in the relevant regulations.

Only the IRB-approved and validated ICF(s) (see below) may be used to enroll subjects. PIs may not execute a sponsor’s ICF in addition to the IRB-approved ICF.

All ICFs validated by the IRB will have two (2) dates; the “Approved” date, which is the date of IRB approval, and the “Valid Until” date. The valid until date is the date set by the IRB for completion of continuing review.

Upon receipt, the validated ICF(s) may be copied and used until the stated expiration date. This procedure helps ensure that only the current IRB-approved ICF(s) are presented to subjects. It also serves as a reminder to the PI and the research team of the need for continuing review.

5.0.1 Elements of Informed Consent

The IRB will ensure that the required elements of consent, per 45 CFR 46.116 and 21 CFR 50.25, are present in the approved ICF and that it provides adequate information to the subject or his/her legally authorized representative regarding the following:

- A statement that the study involves research, an explanation of the purpose of the research, the expected duration of participation, a description of the procedures, and identification of any experimental procedures;
- A description of any reasonably foreseeable risks or discomforts;
- A description of any benefits to the subject or to others that might be reasonably expected from the research;
- Disclosure of appropriate alternative treatment or courses of action, if any, which may be advantageous to the subject, including no treatment or not participating;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that records may be examined by the sponsor, the IRB, the FDA, or other regulatory agencies;

56 FDA: Screening Tests Prior to Study Enrollment – Information Sheet Guidance for IRBs and Clinical Investigators

57 OHRP Informed Consent Checklist – Basic and Additional Elements

58 FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators
For research involving greater than minimal risk, an explanation as to whether compensation and/or medical treatment are available in the event of research-related injury. If so, where further information may be obtained.

The ICF must also identify whom to contact for answers to questions about the research and research subjects’ rights, and whom to contact if the subject sustains a research-related injury;

A statement that participation is voluntary, that the subject may discontinue participation at any time, and that refusal to participate or withdrawal will not involve a penalty or loss of benefits to which the subject is otherwise entitled.

The IRB, when appropriate, will also consider whether the following additional elements of informed consent are required and whether they are adequately included in the ICF(s):

- A statement that the particular procedure or treatment may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant or is a man capable of fathering a child) that are known or currently unforeseeable;

- Anticipated circumstances under which the subject’s participation may be terminated by the PI without regard to the subject’s consent;

- Any costs, or additional costs, to the subject that may result from participation in the research, including whether such costs may be billed to a third party payor (i.e. health insurance);

- The consequences of the subject’s decision to withdraw from the research and procedures for safe and orderly termination of participation;

- A statement that significant new findings developed during the course of the research, which may relate to the subject’s willingness to continue to participate, will be provided to the subject;

- The approximate number of subjects involved in the study at the institution(s).

- Clarification whether the investigational drug, device, or biologic involved in a study will be available to a subject after the subject has completed the study, or if the study is terminated.

- An explanation of the payment plan, or statement that subjects will not be paid for participation.

- An estimate of any hazard associated with exposure to ionizing radiation as a result of participation in the study. The assessment should be in lay language and contextualize the exposure (e.g., a multiple of the background radiation to which people are exposed in one year).

- A statement as to whether human genetic/research testing is associated with the protocol, and if so an explanation of potential relevant risks to the subject and relatives.

The IRB has prepared a template ICF for adult research subjects. This template provides detailed information regarding elements of informed consent and provides recommended language for the ICF. It is strongly recommended that the individual preparing the ICF consult and follow this template.
5.0.2 Informed Consent Witness Signature

Effective 18 November 2003 the IRB EC implemented the following institutional policy:

- New study applications submitted to the IRB for review do not require a witness signature on the ICF.\textsuperscript{59}
- For existing approved protocols that are actively enrolling subjects, the witness signature requirements remain in effect until the PI requests, and receives approval from the IRB, to eliminate the witness signature requirement.

Depending on the level of risk, the nature of the study or the particular study population, the decision to require a witness signature would be made by the IRB Chair, Vice-Chair, or designee, or the convened IRB.

The PI may opt to have the consent procedures witnessed, even if not required by the IRB. If the validated ICF contains a witness signature line, the PI will be expected to have the process witnessed and obtain the witness’s signature.

5.0.3 Re-Consent

Under certain circumstances it may be necessary for subjects to re-consent to participate in a study. The IRB will consider the need to re-consent on a protocol-by-protocol basis or a case-by-case-basis.

The following are among the situations when the IRB may require a subject be re-consented:

- A minor was enrolled in a study and s/he attains age eighteen (18) years while still in the study. The subject would legally be an adult and his/her consent would be required to continue participation in the study, and as applicable, consent would be required for optional tissue banking and genetic testing.

When minors may be enrolled in a study and could have specimens banked and genetic testing performed on them, the protocol is to include a plan to contact subjects enrolled as minors who attain age 18 years to inform them of the study. Such individuals might not be located; in such case, the PI will be instructed to document that reasonable efforts to contact and inform the individual were made. The PI should be advised that failure to obtain consent at age 18 years may hamper future research on banked samples, as at age 18 years subjects must consent to tissue banking and genetic testing or be able to withdraw their samples from being banked. The investigator should include an explanation for what will happen to banked specimens if the subject cannot be reached when the subject reaches the age of majority. It is the IRB’s preference that in these instances, the existing tissue be fully de-identified.

- An individual was temporarily incompetent when initially enrolled in a study, or was enrolled in a study conducted in an emergency setting.

\textsuperscript{59} In the course of review of a protocol the IRB will assess the level of risks to subjects and the complexity of the study and decide whether inclusion of the witness signature adds additional protection or value. Under certain circumstances the IRB may require that the informed consent procedures be witnessed, e.g., enrollment of a vulnerable population, when the study is extremely complex.
A subject participates in a longitudinal study. If the study is particularly long, re-consenting the subject may be necessary to maintain a subject’s understanding of the relevant research activities. Investigators should present a plan for maintaining informed consent when submitting protocols where subjects will be followed over long periods of time.

The research has changed, or important new information relevant to the subject’s continued participation is discovered. Investigators should address whether re-consent is necessary at time of discovering new information, submission of AEs, or protocol amendment.

5.0.4 Responsibilities for Reviewing ICF(s)

An IRB Coordinator may perform an initial screening of the ICF(s) in the context of the proposed research. To the extent possible, the IRB Coordinator will notate the ICF with suggested language, inconsistencies between the ICF and protocol, etc. This notated ICF should then be supplied to the primary reviewer, and if the research is reviewed by the convened IRB, the IRB members and the secondary reviewer.

It is the responsibility of the primary and secondary reviewer to review the ICF(s) as described elsewhere in this manual.

5.0.5 Documentation and Waiver of Informed Consent

In accordance with 45 CFR Part 46.117 and 21 CFR 50.27, except as provided below, informed consent must be documented by the use of a written ICF approved by the IRB and signed by the subject or the subject’s legally authorized representative.

The original signed ICF(s) is to be kept by the PI in a secure location for a minimum of eight (8) years, or more if required by the FDA or sponsor, following completion of the research. For an active, on-going research study, the PI should be able to access ICF(s) in a reasonable amount of time, if requested. A copy of the executed ICF(s) is to be given to the person signing the ICF(s). When the study involves treatment intervention the institutions recommend that the PI also file a copy of the subject’s executed ICF in his/her medical record.

Per 45 CFR 46.117(b) the ICF may be either of the following:

- A written ICF that embodies the elements of informed consent required as outlined in this manual. This ICF may be read to the subject or the subject's legally authorized representative. In either case, the PI/research team is to give either the subject or the subject's legally authorized representative adequate opportunity to read it before it is signed;

or

- A short form written ICF stating that the elements of informed consent required by 46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there is to be a witness to the oral presentation. Also, the IRB is to approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness is to sign both the short form and a copy of the summary. The person actually obtaining consent is to sign a copy of the summary. The PI is to keep the original signed documents and copies of the documents are to be given to the subject or the subject’s legally authorized representative.
While FDA regulations do not permit modifications or waivers of informed consent requirements, except for emergency use of test articles, which are exempt from prior IRB review (refer to other sections of this manual), HHS regulations (45 CFR Part 46.117(c)), permit the IRB to waive the requirement for the PI to obtain a informed consent for some or all subjects if the IRB finds and documents that either of the following are true:

- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subjects’ wishes will govern.

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

45 CFR 46.116(c) allows the IRB to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent outlined elsewhere in this manual, or waives the requirement to obtain informed consent provided the IRB finds and documents that:

- The research or demonstration project is to be conducted by or 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 or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

- The research could not practicably be carried out without the waiver or alteration.

The IRB is also permitted to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent outlined elsewhere in this manual, or waive the requirements to obtain informed consent provided the IRB finds and documents that (45 CFR 46116(d)):

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

- The waiver or alteration will not adversely affect the rights and welfare of the subjects;

- The research could not practicably be carried out without the waiver or alteration; and

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

Waiver of documentation of informed consent, or alteration, will be granted on a case-by-case basis at the discretion of the IRB Chair, Vice-Chair, designee, or convened IRB. In such cases, the IRB may require the PI to provide subjects with a written statement/summary explaining the research. This waiver will be documented for protocols approved by expedited procedures, and documented in the minutes for protocols approved by the convened IRB.
5.0.6 Short Form Use

5.0.6.1 Introduction/Background

When enrolling a non-English speaking person into a study, the informed consent information needs to be presented in a language understandable to the subject and documented (DHHS: 45 CFR 46.116 and 45 CFR 46.117, FDA: 21 CFR 50.25 and 21 CFR 50.27).

The 2 main options for written consent are:

1. The entire written IRB-approved English ICF may be translated into the language understandable to the subject.
   
   **OR**
   
2. A "short form" may be used.

If a study will enroll only a specific non-English speaking population, translation of the entire IRB-approved English ICF is required. Also, if it is expected that more than five (5) persons of a specific non-English speaking population will be enrolled, an ICF in the specific foreign language should be developed for use.

5.0.6.2 Use of a Translated Short Form

To ensure that non-English speaking persons are not excluded from participating in research a “short form” may be used. At Tufts MC/TUHS every study is eligible to use a short form ICF unless the IRB specifically determines to not permit the use of a short form as it relates to a particular study. Under certain circumstances, the IRB may determine to not allow the use of a short form ICF, for example based on the level of risk associated with the study (e.g., a gene transfer research study). Use of a short form is allowed unless specifically stated otherwise in the Tufts MC /TUHS minutes and Notice of IRB Approval letter.

A signed short form basically documents the oral presentation of the entire written IRB-approved English ICF in a language understandable to the subject. For industry sponsored research, PIs are advised to confer with the sponsor prior to the enrollment of a non-English speaking subject and obtain the sponsor’s support for such an enrollment.

The IRB has approved an English short form for use at Tufts MC and TUHS and has had the document translated to several languages and posted on the IRB website. Up to 5 short forms in the same language may be used in a study in a twelve (12) month period.

As with consent of English speaking persons, the IRB will count every subject who has signed a short form as enrolled, whether or not that subject completes the study. That is to say, that each signed short form “counts” toward the five (5) that may be used in a study in a 12 month period.

To help a non-English speaking subject get translation help to telephone the PI, if needed, the IRB has also created and translated a short page called “Directions for help to speak with a research study PI.” This page should be given to the enrolled subject in a language s/he understands.

When using a short form with a non-English speaking person, all of the following must be completed:
The subject must be given a copy of the short form in the language understandable to him/her to read.

A translator/interpreter who is fluent in the subject’s language and English must orally present the entire IRB-approved English ICF to the subject in the language understandable to the subject.

Note: A family member of the subject can act as a translator/interpreter. If a member of the research team is fluent in the language understandable to the subject and English s/he can act as the translator/interpreter and the Person Obtaining Consent; however, s/he may not also act as the witness.

The entire consent process must be witnessed by an individual who is fluent in both English and the language understandable to the subject.

Note: The witness may be staff, the translator/interpreter, a family member, or another person. A member of the study staff acting as translator/interpreter and Person Obtaining Consent is not to also serve as the witness. Before starting the consent process, the PI is to verify whether the translator/interpreter will also be able to serve as a witness. If not, another person will be needed to serve as the witness.

The IRB-approved English ICF must be signed by the investigator authorized to obtain consent and the witness to the consent process.

The short form in the language understandable to the subject must be signed by the subject, the investigator authorized to obtain consent, and the witness to the consent process (see 2 above).

The subject must be given signed copies of both the IRB-approved English ICF and the short form in the language understandable to the subject; and

The original signed English ICF and the original signed short form should be placed in the subject's research record and a copy of both placed in his/her medical record, if appropriate.

During the consent process the translator/interpreter should briefly explain the consent process to the prospective subject. The prospective subject’s questions or concerns should be relayed by the translator/interpreter to the person obtaining consent, and the answers translated back to the prospective subject. Adequate time should be afforded the participant to make an informed decision regarding participation in the study.

Investigators are also advised to consult federal guidance on this topic if in doubt.60 61

60 FDA: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors
61 OHRP: Obtaining and Documenting Informed Consent of Subjects Who do not Speak English, November 9, 1995
5.0.7  Informed Consent for Subjects Who do not Understand English

When an investigator plans to enroll a subject population that does not understand written English the IRB-approved ICF is to be translated into a language understandable to the subject (see section Translation of Study Documents).

In the event of unplanned enrollment of a subject who does not understand written English, the institutions strongly caution investigators to carefully consider the ethical/legal implications of enrolling subjects who do not understand English. If the subject does not understand the information presented, the subject must not be enrolled in the study.

In the event of unplanned enrollment of a subject who does not understand English, federal regulations (45 CFR 46.117(b)(2), 21 CFR 50.27) permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. The oral presentation and the short form written document should be in a language understandable to the subject. The IRB-approved English language ICF may serve as the summary. An impartial third party fluent in both English and the language of the subject is to witness the entire consent process. The short form must be approved by the IRB prior to its use.

The subject or the subject's legally authorized representative is to sign the short form document. The person who obtains consent is to sign a copy of the summary (e.g., the English language ICF). The witness is to sign the short form document and the summary. The impartial third party witness is to sign the consent document. When a translator assists the person obtaining consent, the translator may serve as the witness.

The subject must be given copies of the signed short form document and the summary.

The PI should record a detailed summary of the enrollment of such subjects in the study files and report the enrollment to the IRB and sponsor, if applicable.

The IRB must receive a copy of all foreign language versions of the short form document and any other translated documents presented to the subjects as a condition of approval. Expedited review of these versions is acceptable if the protocol, the full English language ICF, and the English version of the short form document have already been approved by the IRB.

5.0.8  Enrollment of persons who understand English but are Unable to Talk or Write or are Illiterate

Persons who speak and understand English, but cannot not read and/or write, may be enrolled in a study by "making their mark" on the ICF. This includes persons who are illiterate as well as persons who are

62 OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English
63 FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators
64 OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English
65 FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators
physically unable to talk or write but are competent and able to indicate approval or disapproval by other means.

If a person is physically unable to talk or write but is competent, able to understand the concepts of the study, and able to evaluate the risk and benefit of being in the study when it is explained verbally and is able to indicate approval or disapproval to study participation, the person may be enrolled into the study. In such a case, an impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the process is recommended, per FDA guidance. If an investigator chooses to tape the consent process, they must obtain IRB approval for the taping, and the subject must consent to the taping. The investigator should keep the tape on file with the other study documents.

Alternatively, if an individual is physically able to talk or write but is illiterate, federal regulations (45 CFR 46.117(b)(2), 21 CFR 50.27) permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. The oral presentation and the short form written document should be in a language understandable to the subject. The IRB-approved English language ICF may serve as the summary. An impartial third party is to witness the entire consent process.

The name of the subject should be printed on the short form document and after the verbal presentation the subject is to “mark” it, e.g., with an “X.” The witness is to sign the short form document and the summary. The person who obtains consent is to sign a copy of the summary. When a translator assists the person obtaining consent, the translator may serve as the witness. The impartial third party witness is to sign the consent document.

The subject must be given copies of the signed short form document and the summary.

The PI should record a detailed summary of the enrollment of such subjects in the study files and report the enrollment to the IRB and sponsor, if applicable.

The IRB is to receive a copy of the short form document. In addition, the IRB must approve a written summary of what is to be presented orally and the protocol must include a discussion on how the verbal consent process will be carried out.

The IRB expects the PI and study staff to be extra vigilant when an illiterate person is enrolled in a study and must ensure that the subject clearly understands study instructions during the course of the study.

Any subsequent revisions to the ICF must be explained and witnessed in a similar manner.

5.1 Translation of Study Documents

21 CFR 50.20 and 45 CFR 46.116 and 46.117 require that study-related information that is given to a subject or a subject’s legally authorized representative be in language understandable to the subject or the representative.

When the investigator plans to regularly enroll non-English speaking subjects, documents should be prepared in the applicable native language. These documents must be approved by the IRB. Federal
guidance\textsuperscript{66, 67} provides no specific details about how the IRB should verify that the document is intelligible to the subject and/or is culturally sensitive.

This policy applies when part or all of a prospective study population does not speak or read English, or speaks or reads it with minimal facility.

The IRB will review and approve the English version of the document(s) (e.g., ICF, advertisements, patient education material, contact letters, questionnaires, etc). The review may be either expedited or by the convened IRB, depending on the nature of the material and in accordance with federal guidance and regulations. All documents must satisfy IRB standards for language reading level and required elements of consent, etc. The IRB-approved and validated English document(s) may then be translated into the subject’s primary language. The translated material should then be back translated into English to confirm that the meaning has not been changed.

All translated documents, a copy of the approved English versions, and the qualifications of the translator (see below) are to be submitted to the IRB for review. If approved, validated copies of the translated documents will be sent to the PI for use.

The investigator may not use the translated documents (ICFs, advertisements, patient education material, contact letters, etc.) until they are approved and validated by the IRB.

In addition to standard ICF elements, special issues regarding translated documents include that the language be at a reading level appropriate to the subject. For studies being conducted with subjects with a lower literacy level than the eighth grade, a lower reading level may be required. Language choice should be culturally sensitive to the population expected to read the document.

A member of the research team may translate approved documents into another language; however, the back translation is to be performed by someone independent from the research team.

\textbf{5.1.1 Qualifications of translators}

Certifications should be submitted when available. If no certification is available, a cover letter should be provided outlining the translator’s qualifications and their relationship to the study. Qualifications will be evaluated by the IRB on a case-by-case basis.

Documents prepared by professional translation services will be considered based on the quality assurance procedures utilized by the service. The Chair or Vice Chair reviewing these procedures will determine if they meet the institutional standards.

The IRB recommends that the cost of document translation services be included in study budget development.

\textsuperscript{66} OPRR guidance, Obtaining and Documenting Informed Consent of Subjects who do not Speak English,

\textsuperscript{67} FDA Guide to Informed Consent – Information Sheet Guidance for IRBs and Clinical Investigators
5.2 Vulnerable Populations

Federal regulations require that special consideration be given to protecting the welfare of particularly vulnerable participants, such as children, prisoners, pregnant women, and incompetent persons. The IRB will also ensure that appropriate consideration and protections are applied to other potentially vulnerable populations such as incompetent persons, students, and employees not explicitly stated in the federal regulations.

5.2.1 Women and Minorities in Research

The IRB will not unnecessarily exclude women or other subject populations from research.

Women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes exclusion. Exclusion under other circumstances may be made based upon a compelling rationale and justification. The IRB will not recognize cost as an acceptable reason for exclusion except when the study would duplicate data from other sources.

Woman of child bearing potential must not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subject of all ages.

The inclusion of women and members of minority groups and their subpopulations should be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects.68 69 70

Women may be enrolled in any type of research, including Phase 1 and early Phase 2 studies.71 According to the FDA, early drug and biologic studies can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy as well as measures to prevent pregnancy during exposure to investigational agents. When women will be enrolled in a study, the IRB will give special consideration to pregnancy testing. Women should be counseled about the reliable use of contraception or abstinence from intercourse while participating in a study, as appropriate. The type of contraception to be used should be outlined in the protocol, and should be determined in consultation with the woman, the PI and/or her health care provider. These provisions should be outlined in the ICF and protocol.

68 Inclusion of Women and Minorities As Participants In Research Involving Human Subjects - Policy Implementation Page, NIH Guidance, Inclusion of Women and Minorities as Subjects in Clinical Research

69 NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research - Updated August 1, 2000 August 2001

70 NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October 2001

For many approved substances, current information regarding drug effects in pregnancy and lactation is available through accepted databases such as Reprotox. When such information is available, it should be included in the ICF, and updated as necessary. When preclinical teratology and reproductive toxicology data are not available, the PI should ensure that male and female subjects are informed about the potential effects of the test agent on conception and fetal development. All study subjects should be provided with new pertinent information arising from preclinical studies as it becomes available, and the ICF should be updated when appropriate. Study subjects should also be informed about any new clinical data that emerge regarding general safety and effectiveness, including relevant gender effects.

Many investigators seek provision for obtaining information regarding pregnancies in female partners of male study subjects who conceived while the study subject was taking the study agent. If the investigator feels that this may place the partner or future child at risk, consideration should be given to providing written information to the partner at the time the subject is enrolled. If so, this information sheet must be reviewed and approved by the IRB. Similarly, if the partner does conceive, and the investigator would like information about the pregnancy, an IRB approved information sheet should be given by the subject to the partner, offering the partner the opportunity to consent to release information. Partners of study subjects are not research subjects and cannot be required to release information and the investigator cannot directly contact the partner.

5.2.2 Pregnant Women, Human Fetuses and Neonates

The IRB will review research involving pregnant women, fetuses, or neonates in accordance with federal regulations (45 CFR 46, subpart B) and state statutes.

The Massachusetts Fetal Research Statute (M.G.L ch.112, section12J)\(^{72}\) limits research on neonates (minors under 30 days of life). M.G.L. ch.112, section12J states “this section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is to determine the life or health of the fetus involved or to preserve the life or health of the fetus involved or the mother involved.” This is assessed at time of study review, and appropriate findings are made and documented. To aid in the IRB’s determination, the investigator is encouraged to include an explanation of how the research is in conformity with the statute in a cover letter at time of study submission. In practice, findings related to M.G.L. ch.112, section12J are made prior to federal findings, as unless the state statute provisions can be satisfied, the research cannot be performed.

Findings will be made and protocol-specific justifications for discussion at a convened IRB meeting and will be documented in the IRB meeting minutes.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not

\(^{72}\) The General Laws of Massachusetts, Title XVI. Public Health, Chapter 112: Section 12J. Experimentation on human fetuses prohibited; medical procedures authorized; consent; approval; civil and criminal liability and proceedings; severability
greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent requirements described elsewhere in this manual;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children, as defined elsewhere in this manual, who are pregnant assent and permission are obtained in per federal regulation;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

When neonates of uncertain viability and nonviable neonates may be involved in research, all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

Until it has been determined whether or not a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

1. The IRB determines that:

   (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained as discussed elsewhere in this manual, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

After delivery, a nonviable neonate may not be involved in research unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained as discussed elsewhere in this manual, except that the waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate is sufficient to meet the requirements, except that the consent of the father does not need to be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not be sufficient to meet the requirements.

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

In accordance with 45 CFR 46.206, research involving the placenta, the dead fetus or fetal material, macerated fetal material, or cells, tissue, or organs excised from a dead fetus, after delivery, will be conducted only in accordance with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above is recorded for research purposes such that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects. As a result, a separate research application must be submitted to the IRB for review and approval.
5.2.3 Minors

Children are defined as persons “who have not attained the legal age for consent to treatments or procedures involved in the research.” Under Massachusetts law, children are individuals less than 18 years of age (with the exception of emancipated minors and neonates 30-days and younger). Studies involving children are strictly regulated. When reviewing a protocol including children, the IRB must classify the research into 1 of four (4) categories. The minutes must document the category under which the protocol is approved. The four categories of research involving children (category 4 is not approvable by the IRB), based on degree of risk and benefit to individual subjects, are as follows:

45 CFR 46.404, 21 CFR 50.51 — Research not involving greater than minimal risk.

45 CFR 46.405, 21 CFR 50.52 — Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants can be approved only if all of the following are true:

- The risk is justified by the anticipated benefit to the subjects.
- The relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

45 CFR 46.406, 21 CFR 50.53 — Research involving greater than minimal risk and no prospect of direct benefit to individual participants can be approved only if all of the following are true:

- The risk represents a minor increase over minimal risk.
- The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations.
- The intervention or procedure is likely to yield knowledge about the subjects’ disorder or condition that is of vital importance for the understanding of the participant’s condition.

45 CFR 46.407, 21 CFR 50.54 — Research that does not fall into 1 of the three (3) categories above, but which the IRB finds presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children cannot be approved by the IRB acting alone, but requires the approval of the Secretary of the DHHS.

NOTE: The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) does not participate in the activities being observed.

In accordance with federal regulations (45 CFR 46.408, 21 CFR 50.55) the IRB must ensure that the study includes procedures for obtaining the assent of the child as well as the permission of the parent(s) or legal guardian(s). Assent refers to a child’s agreement as distinct from consent, which is legally valid.

Per institutional policy, the assent of a minor is to be solicited if the minor is aged seven (7) years or older, and is of appropriate maturity and psychological state. A minor has the right to refuse to participate.
However, if the IRB determines that the capability of some or all of the minors is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord federal regulations.

Taking into account the age, maturity, and psychological state of the minor involved, she/he is to be provided with an explanation of what participation will involve and given the opportunity to read the ICF(s). A sample minor assent document has been developed by the IRB, and is available on the IRB website. The minor’s assent is to be documented on the ICF, or on a separate assent form.

In certain instances, a minor legally may be considered an “emancipated minor” (e.g. a pregnant minor) and may consent on his/her own behalf without parental involvement. These instances are evaluated on a case-by-case basis, and frequently require obtaining legal advice. Considerations given to approval of an emancipated minor consenting for research include the nature of the research, potential benefit of the research, and potential harms in seeking a parent or guardian’s approval, and applicable state laws.

After review of the information submitted by the PI, it is the responsibility of the IRB to determine whether the consent of 1 parent/guardian or 2 parents/guardians is required:

In accordance with 45 CFR 46.404, 21 CFR 50.51 and 45 CFR 46.405, 21 CFR 50.52 the consent of 1 parent/guardian and the minor’s assent is sufficient.

In accordance with 45 CFR 46.406, 21 CFR 50.53 and 45 CFR 46.407, 21 CFR 50.54, the consent of two (2) parents/guardians and the minor’s assent is required.

Where consent is to be obtained from both parents/guardians, both parents/guardians must give their permission unless 1 parent is deceased, unknown, incompetent, or not reasonably available, or when only 1 parent has legal responsibility for the care and custody of the child.

At its discretion, the IRB may require the signature of 2 parents/guardians in particular situations even though 1 signature is sufficient under the regulations.

Federal regulations (45 CFR 46, subpart B)

5.2.4 Employees and Students

Pursuant to federal regulations, informed consent must be sought in circumstances whereby the possibility of coercion or undue influence of the prospective subject is minimized. The institutions consider employees and students to be vulnerable subject populations.

Consequently, the IRB must ensure that a PI who plans to actively recruit students and/or staff clearly defines the rationale for such participation. In addition, all recruitment strategies must be stated.

When employees and/or students will be enrolled, a letter from the appropriate institutional official (e.g., Dean, Department Chair, Vice-President) attesting to the fact that the project is acceptable and that

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73 21 CFR 50.20, 45 CFR 46.116
coercion has been minimized will be a condition of approval. If residents or fellows are to be enrolled in research, the Program Director is to provide the IRB with a letter of support. This letter must be from an institutional official not involved in the research (e.g., if the program director is conducting research on residents, the letter must come from the department chair or institutional official for graduate medical education).

Of special consideration for the employee and student population is the issue of confidentiality of research study data. Depending on the nature of the research and the data collected, a breach of confidentiality could affect a person’s employment, career path, educational plans, or social relationships within the hospital/school community. The IRB will give special consideration to the PI’s proposed plan for data security.

5.2.5 Prisoners

In accordance with 45 CFR 46.107 and Subpart C (45 CFR 46.301-306) and 21 CFR 56.107, 111, when the IRB reviews research involving prisoner-subjects, at least 1 of the members who participates in the review of the research will be a prisoner or prisoner representative with appropriate background and experience to serve in that capacity. In situations where a particular research project is reviewed by more than 1 IRB, only 1 IRB need satisfy this requirement.

"Prisoner" is defined to include any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Our IRB is not constituted to routinely review research involving prisoners, as it does not have a prisoner or prisoner representative as a regular member. Investigators planning research on prisoners should contact the IRB early in the planning process so that appropriate arrangements may be made for review.

5.2.5.1 Permissible Research

The IRB must find and document in the minutes that the research is within a permissible category under 45 CFR Part 46.306(a)(2), which includes:

Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.

Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults). The study may proceed, however, only after the Department of Health and Human Services (DHHS) has consulted with
appropriate experts including experts in penology, medicine and ethics, and published notice, in the Federal Register, of its intent to approve such research.\footnote{For non-DHHS-supported research, the OHRP recommends that the research proceed only after the IRB has consulted with appropriate experts, as determined by the IRB.}

Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the subject. If the research involves a control group whose members may not benefit from the research, the study may proceed only after DHHS has consulted with the appropriate experts discussed above.\footnote{For non-DHHS-supported research, the OHRP recommends that the research proceed only after the IRB has consulted with appropriate experts, as determined by the IRB.}

### 5.2.5.2 Additional Findings

In reviewing the research proposal, the IRB must make and document the following determinations:

Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.

The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.

Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the PI provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

The information is presented in language that is understandable to the subject population.

Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

### 5.2.6 Decisionally Impaired

The IRB has the responsibility to exercise heightened inspection and to consider additional protections when reviewing research on subjects who suffer from temporary or permanent mental disorders that may affect their decision-making capacity.

Mentally impaired may be defined as persons with either a psychiatric disorder or a development disorder. Others may include persons under the influence of, or dependent, on drugs or alcohol, and those suffering from degenerative disease affecting the brain, or those in a comatose state. Within this category of subjects, there are those individuals who are “free living” and those who are institutionalized.
Institutionalized persons are those individuals residing, whether by voluntary admission or involuntary confinement, in institutions for the care and treatment of the mentally disabled. Such individuals include, but are not limited to, subjects in public or private mental hospitals; psychiatric subjects in general hospitals, inpatients of community mental health centers, and mentally impaired individuals who reside in halfway houses or nursing homes.

Note: Massachusetts law regulates the involvement of clients of the Department of Mental Health in research protocols.

In addition to the mentally impaired, some persons may, as a result of a stroke, head injury, or other acute condition, temporarily or permanently have a diminished capacity to understand the information presented and to make a reasoned decision to participate in research.

It is IRB policy that only persons who are competent, i.e., those with the capacity to provide an informed consent to participate in research, may be enrolled in a protocol, unless the PI has explicitly requested, and the IRB has explicitly approved, enrollment of incompetent persons. The IRB will carefully examine studies designed to provoke symptoms, to withdraw subjects from therapies, to use placebo controls, and when standard therapy is withheld for all or a portion of the duration of the study.

The IRB will consider the following when considering studies seeking to enroll temporarily or permanently incompetent persons:

- The number of subjects to be enrolled and the biological or social attributes that will define their eligibility for participation in the protocol. The IRB will seek an explanation of the rationale for including those subjects considered mentally impaired or otherwise incompetent. Suitable justification may include the following:

  - The purpose of the research is to develop knowledge that one can reasonably expect could benefit the class of persons that the subject represents
  - The research is designed to study the safety and efficacy of a therapeutic modality that is likely to bring direct benefit to the individual subject
  - Preliminary studies already have been performed on less vulnerable subjects
  - The protocol is designed to study conditions that do not affect less vulnerable populations

- The research may not present greater than minimal risk to the subjects, unless the research offers the prospect of direct benefit to each individual subject. Modifications in criteria for review and consent procedures may be required depending on the level of risk and the prospect for benefit to the mentally disabled subject.

- Prior to enrollment of persons with diminished capacity, the PI must determine whether the subject is competent to provide informed consent. Competence may be defined as an ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to express a choice. In some cases, the IRB may request that a person(s) independent from the research study evaluate the subject to determine competence. The IRB may also require the presence of a consent monitor to assure that the subject(s) understand that they are free to decline to participate, particularly in situations in which purely research interventions may be misunderstood by subjects as treatment.

IRB meeting minutes will record whether the IRB has approved the enrollment of incompetent subjects. The minutes may include as necessary additional findings of under what circumstances they may be
enrolled, need to re-consent subjects as their level of competence improves, qualifications of person determining degree of competence, need for assent, etc.

5.3 International Research

Any international research that a Tufts MC/TUHS faculty member, employee, student, etc., is involved with must be reviewed and approved by this IRB, in addition to an IRB/ethics committee in the host country, before any research-related activities may begin. Required documents for submission are discussed elsewhere in this manual.

If a Tufts MC/TUHS faculty member, employee, student, etc., becomes involved after the international research has been initiated, approval from this IRB is required at the time of the investigator’s involvement. The PI will be requested to provide a letter specifying when s/he became involved with the international research and the delineating the components of the research that he/she will be involved in; this letter will be part of the IRB study file.

Any human subjects research in which Tufts MC/TUHS investigators are involved, and which would be subject to the federal regulations if it were conducted entirely within the United States, is to comply with the federal regulations for the protection of human subjects in all material respects, unless otherwise waived by this IRB.

The IRB acknowledges that procedures normally followed in the country where the research will take place may differ from those in U.S. federal regulations. Therefore, in accordance with U.S. regulation, research may be approved if “the procedures prescribed by the [foreign] institution afford protections that are at least equivalent to those” outlined in federal regulation. In such a case, the foreign country's procedures may be substituted for the procedures required by the federal regulations.

Any international research that is funded by the FDA must comply with both DHHS and FDA regulations. Approval from an IRB/ethics committee in the host country will be a requirement for approval by the Tufts MC/TUHS IRB.

Per recent DHHS communication, the requirements of HHS regulations must be satisfied for all HHS-conducted or –supported research covered by a FWA regardless of whether the research is conducted domestically or internationally.75

As federal guidance addressing international research is periodically released, Investigators involved in international research are strongly advised to consult federal sources, including the International Compilation of Human Subject Research Protections guidance document.76

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76 International Compilation of Human Subject Research Protections
5.4 Guidelines for the Management of Dental Distance Education Protocols
(version dated 01/16/07, accepted by the Executive Committee 01/23/07)

The Tufts University Vice Provost has determined that student research projects for the Distance Dental Education (DDE) program, when conducted outside of the Tufts University School of Dental Medicine (TUSDM) and TUHS campus, with no use of University funds or resources, do not constitute research activity at TUSDM, but rather constitute research activity at the site where the research is being conducted. As a result, the research is subject to the review and approval of the local IRB where the research is being conducted and does not require Tufts MC/Tufts University Health Sciences IRB review and approval.

If there is related research activity occurring at TUSDM, or elsewhere on the TUHS campus related to the project, such activity must be submitted for review (or acknowledgement of not being human subjects research) by the Tufts MC/TUHS IRB. Only the DDE program research activities conducted at TUHS are subject to Tufts MC/TUHS IRB oversight.

DDE related research falls into several categories.

Research where the only activity at TUHS is the data analysis of de-identified data. For studies of this type, the data must be de-identified as defined by HIPAA. For such projects, it is adequate to submit a cover letter clarifying that the data are de-identified and the research activities are limited to data analysis only. In these instances, if appropriate, the IRB will provide a standard letter acknowledging that it is not human subject research, per the OHRP guidance issued 10 August 2004.

Studies presenting greater than minimal risk, as defined in the Federal Regulations, being performed at a location other than TUHS. Studies being performed by DDE students in private offices out of state or out of country have been determined by the Tufts University Vice Provost as not constituting research activity at TUSDM, but rather constitute research activity at the site where the research is being conducted. For these studies only, the IRB does not need to be notified at all. IRB approval is to be sought from the IRB with local jurisdiction for the research. If the investigator requires acknowledgement that this research has been determined not to be under the purview of the Tufts MC/TUHS IRB, a cover letter may be sent to the IRB requesting such acknowledgment.

Minimal risk, as defined in the Federal Regulations, studies performed at a location other than TUHS. The Tufts University Vice Provost has determined that upon request the Tufts MC/TUHS IRB may review and assume oversight jurisdiction of these studies where there is no IRB with jurisdiction over the research site. In these instances, a complete IRB application must be submitted for review and approval. An initial determination will be made as to whether the study constitutes minimal risk, as defined by the Federal regulations. If it is minimal risk, it will be reviewed as per the usual IRB procedures. If the study is determined to be greater than minimal risk, the request may be referred to the institutional officials for assessment.

Research where the majority of the research is performed at a location other than TUHS, but a component is performed at TUHS. In this case, appropriate application materials for the research being conducted at TUHS must be submitted to the Tufts MC/TUHS IRB, where it will be reviewed as per the usual IRB procedures.

Of note, other than category 3 and certain instances of category 4 above, a full application is not necessary.
5.5 Use of Stable Isotopes in Investigational Metabolic Studies

In 2001 a subcommittee was formed to determine the safety procedures for administration of stable isotopes to human volunteers. On 27 March 2003 the IRB EC reviewed and adopted the subcommittee’s recommendations, which are delineated below.

The subcommittee considered stable isotope safety in three domains:

1. Isotope effects
2. Chemical effects
3. Sterility

In addition, the subcommittee considered stable isotopes administered as small molecules, such as water, and as larger molecular tracers, such as amino acids, glucose, etc., given either intravenously or orally. The available literature data and the subcommittee’s own experience was reviewed regarding deuterium (D), 18O, 13C, 15N, and natural Br. 77

5.5.1.1 Isotope Effects:

The subcommittee determined that these effects are really only documented for deuterated water, and fall into two (2) categories, “solvent isotope effect”, and “deuterium isotope effect.” Because deuterium is twice as heavy as hydrogen, while other tracers are only fractionally heavier than the parent isotope (e.g., 13C vs. 12C, 18O vs. 16O, etc.), the difference in chemical behavior between D2O and H2O is greater than for other tracer-tracee combinations. Solvent isotope effects occur because of D2O’s effects on the structure of water and macromolecules, largely through enhanced hydrogen bonding that occurs when D substitutes for H. Deuterium isotope effects result from the ability of D to replace H in biological molecules. Nevertheless, although C-D bonds have been reported to be as much as 10-fold stronger than the C-H bonds, minimal physiological consequences have been observed. Deuteration of O, N, or S bonds does not have the same effects as C-D bonds (reviewed in Kushner et al., 1999). 78

The effects of D2O have been studied extensively for over 40 years. It is clear that humans and animals tolerate tissue enrichments as high as 20% without ill effects. Animal experiments have shown that enrichments as high as 25% did not affect health, but higher levels caused sterility (see Jones & Leatherdale, 1991). 79 In contrast, studies of body composition and energy expenditure usually increase total body deuterium to < 0.01%, a level that is well below the danger level. Anecdotal reports suggest that at this level of enrichment, the only side effects are transient dizziness and nausea (Jones & Leatherdale, 1991). 80 Based on experience at the HNRCA, transient nausea has occurred after D2O administration in the fasted state, which resolved with feeding. This has also been observed after oral deuterated leucine administration. However, the subcommittee cannot distinguish an effect of the deuterium from the effect of fasting overnight, as similar side effects have occurred with oral methionine administration (without deuterium).

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80 ibid
As noted above, isotope effects do not pertain to any other stable isotopes heavier than deuterium. For example, 90% enrichment with $^{18}$O had no ill effects on rodents over three (3) generations. Since enrichments even 1/10 of that are impossibly expensive to produce in humans, there is no safety issue with non-deuterium isotopes.

### 5.5.1.2 Chemical Effects

This category refers to change in the behavior of molecules because of the addition of a stable isotope, most commonly D or $^{13}$C. There are different pharmacological and metabolic effects to deuterated forms of medications such as cyclophosphamide, amphetamines, and other drugs (Kushner, 1999). However, no such effects have been noted for stable-isotope tracers of amino acids, glucose, and fatty acids. There is a wealth of research experience around the world over the past 4 decades with each of these compounds, without any ill effects reported as long as tracer doses are maintained.

### 5.5.1.3 Sterility

Sterility and pyrogenicity are the main threats to the safety of human volunteers given intravenous stable isotope tracers. Although in the past, investigators prepared their own intravenous solutions, for the past several years all tracers intended for IV administration are prepared by the Tufts MC research pharmacy under sterile conditions. Pyrogenicity has been tested for each batch of tracer at Cape Cod Associates. Oral solutions are not required to be sterile unless given to immunosuppressed patients or delivered post-pylorically where the barrier of gastric acidity is circumvented.

### 5.5.1.4 Recommendations

The subcommittee proposed the following upper limits for routine IRB approval:

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deuterated tracers</td>
<td>1 g of D$_2$O or 0.1 g of D per kg body weight</td>
</tr>
<tr>
<td>$^{18}$O</td>
<td>no upper limit needed.</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>3 mg/kg continuous infusion, 2 mg/kg prime</td>
</tr>
<tr>
<td>NaBr</td>
<td>100 mg of NaBr /Kg body weight (“Additional Information” below)</td>
</tr>
</tbody>
</table>

If studies in the future require higher levels of these tracers, these should be reviewed and approved on a case-by-case basis, and depending on the potential risks of the proposed protocol. For example, deuterated fatty acids have been used to measure fat mass, but required higher doses than the above recommendation. At the time, the subcommittee did not anticipate the use of such doses in the foreseeable future, but such projects should not be categorically excluded given the likely emergence of new methods.

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5.5.1.5 Conclusion

Stable isotope labeled water and tracers are among the safest and most useful means of investigating the metabolisms of animals and humans. Jones and Leatherdale (1991) conclude their review of the safety of stable isotopes by writing, “Approaching half a century of stable-isotope usage in human metabolic studies has been without documented significant adverse effect.”82 Kushner et al (1999) agree with this conclusion and expand upon it: “In purer scientific terms, no apology is needed for the use of deuterated compounds. Their use in studies of drug metabolism is very well established, as is their contribution to studies of other biochemical pathways. The continuing need for this compound [D2O], and for deuterated compounds in general, in physiological, pharmacological, and biochemical studies, cannot be questioned.”83

The IRB will consider all human subject research that employs stable isotopes in investigational metabolic studies in accordance with the findings of the above-referenced subcommittee.

If a stable isotope is used for metabolic tracer studies employing drugs or non-pharmacological substances, such as glucose or individual amino acids, for which there are adequate data demonstrating their safety and if the substances used are within the limits for which the data are adequate, no IND is required. However, IRB oversight and obtaining informed consent are required (waiver of consent could be requested if the investigator feels the protocol meets the common rule requirements for waiver of consent).

5.5.1.6 Additional Information

Natural NaBr is used to measure extracellular water space.

A known amount of natural, stable Br is administered in the form of NaBr solution orally or intravenously (1) as specified in the specific protocol. Bromide will reach equilibrium in the extracellular space in about 3 hours when a blood sample is taken to measure Br concentration in plasma. The method provides a measure of extracellular space after a correction is applied for a small (and assumed constant) fraction of Br that will penetrate the cell membrane.

**Bromide safety:** Bromide has been used by several investigators in adults and children, administered intravenously or orally (as NaBr), without any adverse effects. The solutions used range in concentration from 3-10% and the dose from 29 - 131 mg of NaBr per kg of body weight. Our own experience with adult volunteers (oral dosing at <40mg NaBr per Kg of body weight) has produced no adverse effects.

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Subjects</th>
<th>Solution/(oral or IV)</th>
<th>NaBr dose mg/Kg weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brans / 2</td>
<td>10 Infants</td>
<td>10% IV</td>
<td>94-131</td>
</tr>
<tr>
<td>Finley / 3</td>
<td>45 children</td>
<td>5% IV</td>
<td>100</td>
</tr>
<tr>
<td>Cassady / 4</td>
<td>74 neonates</td>
<td>IV</td>
<td>95</td>
</tr>
<tr>
<td>Miller / 5</td>
<td>6 ill children</td>
<td>IV</td>
<td>64</td>
</tr>
</tbody>
</table>


5.6 Definition of Ionizing Radiation

All X-rays, including Computed Tomography (CT) scan, bone densitometry, mammography, all nuclear medicine procedures, and all radiation therapy procedures, whether they use radioactive sources or external beam (accelerators) emit ionizing radiation. Accordingly, any research that involves exposure to any of these sources of ionizing radiation for research purposes will be forwarded to the convened IRB for review. If the use of the ionizing radiation is for clinical and not research purposes that study may be reviewed by expedited review, provided it is otherwise minimal risk and meets a category of expedited review procedures. If it is not clear whether the use is solely clinical, then the protocol will be forwarded to the convened IRB.
When subjects will be exposed to ionizing radiation for research-related purposes only, the institutional Radiation Safety Officer’s review and approval of the ionizing radiation exposure(s) will be required before final IRB approval may be granted. The Radiation Safety Officer typically suggests appropriate language describing the radiation exposure for the ICF. It is expected that the investigator will include this language in the ICF.

Neither Magnetic Resonance Imaging (MRI) nor ultrasound imaging involves ionizing radiation.

### 5.7 Massachusetts Controlled Substances Researcher Registration

Pursuant to Massachusetts General Law [M.G.L. Chapter 94C, §7](#), all investigators conducting human subject research involving investigational and/or approved drugs for new indications must register annually with the Massachusetts Department of Public Health.

Tufts MC and TUHS have an agreement with the Massachusetts Department of Public Health that provides for only the Department Chair or division chief to possess a valid Controlled Substances Researcher Registration. This registration extends to all the faculty members organized within a registered department.

The IRB office processes applications for Chairs/Chiefs. The Chairs/Chief shall be responsible for completing the necessary Massachusetts Department of Public Health form(s) and the accuracy of the information in said form(s). The original Massachusetts Controlled Substances Researcher Registration is forwarded to each registered Department Chair/Chief, with a copy maintained on file in the IRB office.

### 5.8 IRB Administrative Fee

Administrative fees may be charged to any industry-sponsored human research study to offset the costs of maintaining the IRB office. Institutional leadership will determine the fee(s).

At Tufts MC, the invoice and collection of said fee(s) is the responsibility of the Office of Research Administration. TUHS may also apply a fee to such research studies; however, the application and collection of such a fee is the responsibility of the each academic school.

There is also a Tufts MC/TUHS fee of $750 for studies reviewed by WIRB, in addition to WIRB’s fee schedule. There is no fee for federal/foundation funded studies

### 5.9 Certificate of Confidentiality

A Certificate of Confidentiality protects identifiable research information from forced disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether federal, state, or local.84

On a case-by-case basis the IRB will assess whether a Certificate of Confidentiality is needed; the IRB may require a PI to obtain a NIH-issued Certificate of Confidentiality as a condition of approval in accordance with federal guidance. Such a requirement will be documented by the IRB and will be

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84 National Institutes of Health Office of Extramural Research, Certificate of Confidentiality Kiosk
communicated to the PI. If a Certificate of Confidentiality is obtained, the NIH recommended consent language is to be included in the ICF.

5.10 Subject Complaints

Any communication received in the IRB office from a subject, or forwarded on a subject’s behalf from another source, will be called to the attention of the Manager of IRB Operations or his/her designee. S/he will review the nature of the communication and the IRB Chair, a Vice-Chair, the Manager of IRB Operations, or designee will contact the subject, if required. The PI may also be contacted, if needed, to obtain additional information. A summary of the incident and communications will be recorded in the IRB study file. A subject complaint may, at the discretion of the IRB Chair, Vice-Chair, or designee, be reported to the convened IRB and/or Institutional Official.

5.11 Policy on Investigating and Reporting Research Non-Compliance

A situation involving potential non-compliance may be brought to the attention of the IRB Chair, a Vice-Chair, an IRB member, the Manager of IRB Operations, any of the IRB office team, the Corporate Compliance Office or hotline for Tufts University or Tufts MC, or the Institutional Official for either institution, who will immediately notify the IRB Chair and/or the Manager of IRB Operations.

As used in this policy, non-compliance means failure by a PI or members of the PI’s research team to comply with federal and state regulations, as well as institutional policies and guidelines, for human subject protection or with the requirements or determinations of the IRB.

If potential non-compliance arises in the context of a particular research study, as is usually the case, the IRB Chair and/or Manager of IRB Operations may triage the event as outlined below. If potential non-compliance does not relate to a particular study, the IRB Chair will carry out the tasks below.

The IRB Chair and/or Manager of IRB Operations may also initially interview the individual reporting the potential non-compliance and, if appropriate, the PI and research team, to obtain preliminary information. Based upon this preliminary information, a list of issues and questions will be prepared by the Manager of IRB Operations for discussion with the EC.

The assessment and response to non-compliance will consist of a three-tiered approach, based upon the nature of the event(s) and the potential affect on the safety and/or welfare of human research subjects. Inherent in this approach is the ability to triage, conclude, and act on a non-compliance event in accordance with the institutional timelines set forth in this document.

The three tiers are defined as:

A) Administrative Non-Compliance

B) Non-Compliance of Concern Not Affecting Subject Safety

C) Non-Compliance of Concern Affecting Subject Safety

■ Administrative Non-Compliance

For purposes of this policy, administrative non-compliance does not affect and could not have affected the rights, safety, or welfare of subjects. Examples of Administrative non-compliance include:
1) Use of an outdated informed consent form that is identical to the currently IRB approved ICF, or identical in all material respects (e.g., change in the name of a Co-Investigator).

2) Minor over enrollment of IRB-approved accrual goal in a minimal-risk research study.

3) Delinquent submission of updated protocol, which contains modifications of an Administrative nature only.

The IRB will adhere to the following procedures:

- Initiate Non-Compliance Routing Form (NCRF);
- If required, request written documentation from PI or 3rd party reporter;
- The IRB Chair or designee will review the NCRF and supporting documentation and request further information if required. At this time, the IRB Chair may engage the PI in an active discussion of the intended investigation of the event;
- The IRB Chair or designee will verify that the reported event(s) does not affect the safety of past, current, and/or future subjects;
  - If yes, the Chair or designee will re-triage the event(s) to the appropriate non-compliance level.
- If the event does not affect subject safety, the corrective action(s) will be determined by the IRB Chair or designee;
- The PI will be formally notified of the determined corrective action(s);
- The IRB will be notified of the event and the corrective action(s) determined. The corrective action(s) will be open to comment only. Comments made by the IRB will be recorded and may influence the management of future events. The notification and relevant discussion of non-serious non-compliance events will be documented in the IRB meeting minutes as an attachment.

B) Non-Compliance of Concern Not Affecting Subject Safety

For purposes of this policy, non-compliance of concern not affecting subject safety potentially affects or could have affected the rights or welfare of research subjects, but not their safety. Examples of non-compliance of concern not affecting subject safety include:

1) Significant over enrollment of IRB-approved accrual goal;

2) Significant delinquency in reporting SAE(s) that did not require changes to the ICF.

The IRB will adhere to the following procedures:

- Initiate a NCRF;
- If required, request written documentation or additional information from the PI or 3rd party reporter;
The IRB Chair or designee will review the NCRF and supporting documentation and request further information if required. At this time, the IRB Chair or designee will engage the PI in an active discussion of the intended investigation of the event. Upon conferring with the PI, the IRB Chair or designee may suggest that the PI voluntarily cease the enrollment of new subjects pending resolution of the investigation;

A preliminary investigation may be initiated, whereby the Manager of IRB Operations will interview relevant individuals, including the PI, Clinical Research Coordinator, hospital personnel, and, in appropriate circumstances, research subjects. The Manager of IRB Operations will also review all relevant source documentation, which may include the IRB file, the relevant research records, and the informed consent forms. The Institutional Official(s) may, at his/her discretion, appoint an individual or group from inside or outside the institution to conduct or assist with the investigation.

The IRB Chair or designee will verify that the reported event(s) does not affect the safety of past, current, and/or future subjects;

- If yes, the Chair or his/her designee will re-triage the event(s) to the appropriate non-compliance level.

A meeting may be scheduled that may include the PI, the IRB Chair or designee, the Manager of IRB Operations, the appropriate Institutional Official, and others as appropriate. Legal advice may be sought upon the recommendation of the Institutional Official(s).

Subsequent to consultation with the Institutional Official(s), the event will be discussed at the next EC meeting, at which time corrective action(s) will be proposed. The EC will also determine the level of involvement to be sought by the last reviewing IRB. The PI and/or his/her Department/Division Chair may be invited to attend an EC meeting to discuss the issues.

If the event does not affect subject safety, but is deemed serious in nature, the Institutional Official(s) will be consulted to address the need to report the event to OHRP, FDA, and other appropriate agencies, as required.

- If yes, the appropriate Institutional Official(s) will make an initial telephone report to the federal agency(ies) normally within twenty-five (25) business days from the time the EC renders a determination. The telephone call will be followed by the submission of official documentation to the federal agency(ies) shortly thereafter.

The convened IRB will be notified of the event(s) and the corrective action(s) determined. The corrective action(s) will be open to comment only. All comments made by the convened IRB will be noted and may influence the management of future events. The notification and discussion of non-compliance of concern not affecting subject safety compliance events will be documented in the IRB meeting minutes as an attachment; OR

At its discretion, the EC may opt to refer the non-compliance to the last reviewing IRB, which will actively deliberate and vote upon the corrective action(s) proposed by the EC. The discussion of all controverted issues, deliberation, and votes will be recorded in the IRB meeting minutes, as applicable.
• Following the deliberation of the EC and IRB, the IRB Chair or designee will sign a letter to the PI that describes the following:
  o The specific areas of non-compliance at issue;
  o Any documents that the PI should submit or prepare for submission to the EC; and/or last reviewing IRB;
  o The specific questions requiring response and clarification;
  o Any corrective action(s) to be taken;
  o Any other outstanding issues to be resolved;
  o An invitation may be extended to the PI to attend the EC meeting.

• The PI is responsible for preparing a formal, written response to the correspondence described above. The letter should include an explanation of the event(s), all requested response(s) and clarification(s), and a proposed plan to ensure that similar incidents do not happen in the future. The IRB Chair or designee will provide copies of the PI’s response to the EC and, if so determined, the last reviewing IRB.

• A letter will be sent from the IRB Chair or designee to the PI.

C) Non-Compliance of Concern Affecting Subject Safety

For purposes of this policy, non-compliance of concern affecting subject safety significantly affects or could have affected the rights, safety, and/or welfare of research subjects. Examples of non-compliance of concern affecting subject safety include:

1) Substantial protocol deviations or violations affecting subject safety;

2) Delinquent reporting of serious or unexpected adverse events that would require changes to the informed consent form or protocol or would cause the IRB to consider suspending the study for safety considerations.

The IRB will adhere to the following procedures:

- Initiate a NCRF;

- If required, request written documentation or additional information from PI or 3rd party reporter;

- The IRB Chair or designee will review the NCRF and supporting documentation and request further information if required. At this time, the IRB Chair or designee may engage the PI in an active discussion of the intended investigation of the event. Upon conferring with the PI, the IRB Chair or designee may suggest that the PI immediately and voluntarily cease the enrollment of new subjects pending resolution of the investigation. Additionally, the IRB Chair or designee may choose to invoke the Involuntary Suspension and Termination Policy outlined elsewhere in this manual.
The IRB Chair or designee will verify that the reported event(s) does affect the safety of past, current, and/or future research subjects;

- If no, the IRB Chair or designee will re-triage the event to the appropriate non-compliance level

If the event does appear to be consistent with non-compliance of concern affecting subject safety, the Institutional Official(s) will be consulted to determine the need to report to OHRP, FDA, and other appropriate agencies, as required;

- If yes, the appropriate Institutional Official(s) will make an initial telephone report to OHRP, FDA, and other appropriate agencies, as required normally within five (5) business days, followed by the submission of official documentation to OHRP, FDA, and other appropriate agencies, as required shortly thereafter.

A meeting may be scheduled that will include the PI, the IRB Chair or designee, the Manager of IRB Operations, the appropriate Institutional Official(s), and others as appropriate. Legal advice may be sought upon the recommendation of the Institutional Official(s).

If not already in effect, the policy on Involuntary Suspension/Termination may be invoked, at which time a determination will be made regarding the study specific procedures, if any, which may continue during the investigation;

The event will be discussed at the next EC meeting at which time corrective action(s) will be proposed;

The last reviewing IRB will actively deliberate and vote upon the corrective action(s) proposed by the EC, including the possibility of termination. The issue of reversing a suspension or the potential invocation of the policy on Involuntary Suspension/Termination will be discussed as indicated. The discussion of all controverted issues, deliberation, and vote will be documented in the IRB meeting minutes. The other IRB committee will be notified of the final corrective action(s), etc.

Following the deliberation of the EC and the last reviewing IRB, the IRB Chair or designee will sign a letter to the PI that describes the following:

- The specific areas of potential non-compliance at issue;
- Any documents that the PI should submit or prepare for submission to the EC and/or last reviewing IRB;
- Specific questions requiring response and clarification;
- Any corrective action(s) to be taken;
- Any other outstanding issues to be resolved;
- In most instances, the PI and/or his/her Department/Division Chair may be invited to attend the EC meeting.
The PI is responsible for preparing a formal, written response to the correspondence described above. The letter should include an explanation of the event(s), all requested response(s) and clarification(s), and a proposed plan to ensure that similar incidents do not happen in the future. The IRB Chair or designee will provide copies of the PI’s response to the EC, and if so determined, the last reviewing IRB.

If the study has been suspended, upon receipt of the formal response from the PI, the re-initiation of the research study will be evaluated and determined at the next convened meeting of the last reviewing IRB.

If a final report to a federal agency(ies) and/or a funding agency, the IRB Chair or designee, will prepare that report, with consultation from the appropriate Institutional Official and the Manager of IRB Operations. The report should include:

- An overview of the non-compliance event(s);
- A detailed description of the investigative actions taken;
- A detailed explanation of why the non-compliance occurred;
- The corrective/preventative action(s) that have been or will be taken;
- Sanctions imposed, if any.

If the IRB Chair or designee, at any point in the process, determines that suspension or termination of the study is necessary to protect the safety of study subjects, Sections 1 through 8 of the policy on Involuntary Suspension/Termination should be followed in addition to the sections described in this policy.

The IRB Chair or designee or the appropriate Institutional Official will keep the IRB informed of the status of the non-compliance process, including the substance of the determinations described in Section 6 above, and a summary of the findings of an investigation. All IRB members will be notified of, and have access to, the following items in the IRB office:

- Correspondence to or from the PI setting out the specific areas of potential non-compliance and the PI’s response;
- Correspondence from the Institutional Official to any federal agency(ies) reporting non-compliance and any written response from the federal agency(ies);
- Any other substantive communications from the IRB Chair or designee to the PI regarding the non-compliance event(s).

A PI and research team is expected to cooperate with any non-compliance investigation and to provide any information requested of him/her as part of that investigation. Continued non-cooperation or continued failure to provide requested information may be regarded as serious non-compliance with the requirements and determinations of the IRB.
5.12 IRB Review of Proposed Research Involving Tissue Banking

5.12.1 Introduction

This policy addresses research protocols that propose to collect human biological material (HBM) and store it in a repository for future research use. Such a repository is referred to as a “tissue bank” if the repository accepts and stores HBM for future research uses. The tissue bank may be located within TUHS/Tufts MC or at a remote location.

This policy also addresses information from medical records that could potentially accompany the HBM to be stored in a tissue bank.

5.12.2 Scope of Policy

This policy is intended to apply to situations in which research subjects are asked to consent to the collection of their HBM for transfer to a repository (tissue bank), regardless of the location of the tissue bank, for storage and future research use. The policy does not address the mandatory collection and transfer of HBM to a tissue bank as legally required under state law or regulation. The policy is limited to HBM collected from living persons and does not address the use of HBM obtained post-mortem.

The collection of gametes and fetal tissues raises special issues that are outside the scope of this policy.

5.12.3 Tissue Banking Definitions

The following definitions will be used for the purposes of this policy.

“Human subject” is defined as: “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.” (45 CFR 46.102(f)).

HBM include a full range of specimens, from subcellular structures and cell products such as DNA, to cells, tissue (e.g., blood, bone, muscle, connective tissue and skin), organs (e.g., liver, bladder, heart, kidney, placenta), secretions, and waste (e.g., hair or nail clippings, urine, feces, sweat, or tears that often contain shed skin cells).

Classification of HBM: HBM may be classified according to whether or not the donor of the HBM can be identified. This document will use the following definitions:

Identifiable HBM:

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85 Note: This definition is adapted from the 1999 report of the National Bioethics Advisory Commission entitled “Research Involving Human Biological Materials: Ethical Issues and Policy Guidance.” http://bioethics.georgetown.edu/nbac/hbm.pdf

This is HBM to which observable HIPAA-defined identifiers are attached (see Appendix). The HBM is associated with documented, unhidden individually identifiable health information in such a way that the Source Individual could be identified due to the presence of an unconcealed name, medical record number, clear pedigree location (i.e.: his or her relationship to a family member whose identify is known) or any other HIPAA-defined identifier.

HBM specimens whose HIPAA-defined identifiers have been replaced with a code that is linked to the specimen are considered identifiable HBM. Although readily recognizable information has been replaced by coded information, the presence of a link connecting the original specimen and its recreated (coded) identification could allow a tissue bank or investigator who obtained the code to identify the Source Individual. Thus, coded HBM that is linked to protected identifiers is considered identifiable HBM.

Unidentifiable HBM87:

HBM specimens whose associated, individually identifiable information was never collected or, if collected, was permanently removed and cannot be retrieved by the tissue bank or an investigator obtaining samples from the tissue bank are termed “unidentifiable”. Note: HBM from which identifiable information has been permanently removed is frequently also referred to as “anonymized”.

HBM whose individually identifiable information was replaced with a code is considered unidentifiable if the code was subsequently destroyed.

Code: A system of letters, numbers, or symbols into which normal language is converted to allow information to be hidden, concealed, or communicated secretly; any method used to transform data into an obscured form; the replacement of identifying information (such as name or social security number) with a number, letter, symbol, or combination thereof (i.e., the code)

Coded HBM or coded medical record information (MRI): This term refers to HBM or MRI whose identifying information (such as name or social security number) has been replaced with a number, letter, symbol, or combination thereof (the code); and for which there exists a means or “key” to decipher the code. Deciphering the code would enable linkage of the HBM or MRI to the private information of the donor of the HBM (source individual).

Tissue Bank: An entity that receives, catalogues, and stores HBM, with or without associated MRI, with the intent of making the HBM available at some time in the future for research purposes.

Tissue Banking: Refers to the receipt, storage, and subsequent distribution or use of HBM (with or without HIPAA-defined identifiers) to investigators for research purposes.

Tissue Banking is not Batch Processing: TUHS/Tufts MC regularly reviews research protocols that involve collection and analysis of HBM. Such collection and analysis frequently occurs periodically as the research study proceeds. In many instances, HBM is collected and preserved for analysis, usually with other similarly gathered HBM, at the conclusion of the study or at a convenient and economical point in time during the study. This HBM is either destroyed during the process of analysis or, once the study is concluded, is destroyed. This is the typical scenario when, for example, blood is drawn in conjunction with a research protocol to determine a subject’s serum lipid profile or a subject’s serum level of a particular drug being studied and the blood is set aside for future analysis. This is not tissue banking since the HBM

(blood) is not being held in a repository for future research use, will not be subjected to testing outside the stated purpose and objective(s) of the original research protocol, and will not be disseminated to other investigators who are not part the original protocol.

**Tissue Banked Samples are not Protocol-defined Archived Samples:** A research protocol may clearly explain that some of the HBM acquired for purposes of the study will be archived for subsequent testing at some date in the future. Typically, these archived samples will be used to confirm tests that were previously performed in the study on the same sample. These archived samples are not intended to be used by investigators other than those conducting the original research protocol, are not intended to be subjected to testing outside the stated purpose and objective(s) of the original research protocol, and will not be disseminated to other researchers who are not part the original protocol.

**Archived Samples:** The collection, cataloging, and storing (archiving) of HBM for future analysis that is specifically described in the original research protocol is not “tissue banking”. Until the archived HBM are exhausted or the study is completed and will have no further need of the archived samples, the research study must be kept active and undergo IRB continuing review. Additionally, the expected length of retention of specimens is to be described in the protocol and the ICF.

**Retention of banked and archived specimens:** These are specimens that are being retained in order to be used for purposes other than tissue banking described in an IRB-approved study. The study must be kept active and undergo IRB continuing review until these activities are completed. These specimens are not to be retained past the conclusion of the study. The expected length of retention of specimens is to be described in the protocol and ICF.

**Research:** Is understood as defined in the Common Rule, that is, as a systematic investigation designed to develop or contribute to generalizable knowledge. (45 CFR 46.102(d)).

**Genetic Testing** is the analysis of human DNA, RNA, chromosomes, proteins, and/or certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical or research purposes.

**HIPAA:** Is the Health Insurance Portability and Accountability Act of 1996 as amended and refers to Federal regulations that govern the use or disclosure of protected health information by covered entities (i.e., health care providers, health plans, and health care clearinghouses).

A **Cell Line** consists of cells of a single type (human, animal, or plant) that have been adapted to grow continuously in the laboratory and are used in research or industry.

**Medical Record Information (MRI):** Means information in any medium, including paper or electronic, that is derived from medical records maintained by Tufts MC or Tufts University or from research records maintained by investigators, co-investigators, or other research team members in association with a clinical trial that has been reviewed and approved by the IRB.

**Classification of MRI:** MRI may be classified according to whether or not the patient or research subject to whom the MRI refers can be identified. This document will use the following definitions:

**Identifiable MRI:**
- This is MRI containing unconcealed HIPAA-defined identifiers (see Appendix). Identifiable MRI includes readily observable protected information such that the Source Individual could be identified due to the presence of an unconcealed name, medical record number, clear pedigree location (i.e.: his or her relationship to a family member whose identity is known) or any other HIPAA-defined identifier.
- MRI containing information that has been replaced with a code that is linked to the specimen is considered identifiable MRI. Although readily recognizable information has been replaced
by coded information, the presence of a link could allow a tissue bank or investigator who obtained the code to identify the Source Individual. Thus, coded MRI that is linked to identifiers is considered identifiable MRI.

Unidentifiable MRI:

- MRI from which identifiable information was permanently removed and cannot be retrieved by the tissue bank or an investigator is considered unidentifiable.
- MRI whose identifiable information was replaced with a code is considered unidentifiable if the code was subsequently destroyed.

Source Individual: The living individual from whom the HBM and/or MRI is collected.

5.12.4 Type of IRB Review

Not Human Subject Research: Research conducted with unidentifiable HBM/MRI that were not collected specifically for the currently proposed research through an interaction or intervention with living individuals is not human subjects research and is not regulated by the Common Rule (See 16 October 2008 OHRP Guidance: http://www.hhs.gov/ohrp/policy/edebiol.html).

- In order to deem a given research protocol exempt from IRB review, as defined in 45 CFR 46.101, the IRB must determine that: The HBM/MRI to be used for tissue banking was collected as part of clinical care or as part of the primary clinical research, and
- No additional volume of blood or tissue was obtained in order to provide HBM for tissue banking.

**NOTE:** Research protocols involving the collection, transfer to, and storage in a tissue bank of unidentifiable HBM/MRI must be initially reviewed by the IRB. It is the IRB – not the investigator - that must make the determination that a proposed study does not involve human research.

Exemption from IRB Review: Some tissue banking research may qualify for exemption from IRB review under 46.101(b)(4). To qualify for the exemption, specimens must be in existence at the time the exemption is applied for, and the information must be recorded by the investigator in a way that the subjects cannot be identified either directly or through identifiers linked to the subjects. The investigator must apply for and the exemption must be granted by the IRB before the research can begin.

Expedited Review: As defined by the Common Rule, all minimal-risk research involving HBM/MRI may be eligible for expedited review. (See: http://www.hhs.gov/ohrp/policy/expedited98.html)

Convened Committee Review vs. Expedited Review: Research that is greater than minimal risk requires review by the convened IRB.

5.12.5 IRB Information Requirements

Before the IRB will consider proposed research involving the collection of HBM, with or without associated MRI, that falls within the scope of this policy, the PI of the proposed research must provide the IRB with the following information:

- The name and address of the tissue bank responsible for maintaining the HBM.
• The names, telephone numbers, and e-mail addresses of the contact person(s) at the tissue bank.
• The types of HBM to be transferred to the tissue bank, e.g., blood samples, tumor specimens, etc.
• The manner in which the PI plans to collect the HBM.
• The type and frequency of procedure used to obtain the HBM and the total amount of tissue removed for tissue banking must be stated in the protocol or in a site-specific protocol addendum. For example, the PI may plan to collect HBM by means of an additional procedure, e.g., an additional blood draw or biopsy, that is not part of clinical care or the primary research; or the PI may plan to use a blood draw that is scheduled as part of clinical care or as dictated by the research protocol.
• The protocol or site-specific protocol addendum must specifically state whether an additional volume of HBM will be removed from the research subject for banking purposes and, if this is the case, the volume of the additional HBM to be removed.
• Whether the HBM that the PI proposes to transfer to the tissue bank will be identifiable or unidentifiable.
• If the HBM is to be coded and linked, the name, telephone number, and e-mail address of the person who is responsible for maintaining the link and their relationship to the study, i.e., PI, co-investigator, etc.
• The circumstances, if any, under which the code associated with the link may be revealed.
• If it is planned that the tissue bank will distribute the HBM/MRI for research use by other investigators, whether the materials will be identifiable or unidentifiable when distributed to other investigators.
• Whether the PI also proposes to transfer the Source Individual’s MRI to the tissue bank. If so, a detailed description of the specific information to be transferred must be included in the protocol or in a site-specific protocol addendum. Such information includes, but is not limited to:
  • Whether the MRI that the PI proposes to transfer to the tissue bank will be identifiable or unidentifiable.
  • Whether the information transferred to the tissue bank is.
  • Limited to information that is available at the time the HBM is transferred to the tissue bank, or
  • To be provided on an ongoing basis or at predetermined times in the future. **NOTE:** Predetermined times may be defined in chronological terms (every 6 months) or expressed in terms of a triggering event (visit to an emergency room). In either case, the protocol (or site-specific protocol addendum) and the ICF must define the predetermined times and the duration of information transfer.
• A written explanation of the tissue bank’s policies that govern:
• The types of investigators or entities to whom the HBM/MRI may be distributed, and
The types of research for which the HBM/MRI may be distributed, and

The measures taken to guard against disclosure of the Source Individual’s confidential information.

*NOTE:* A copy of the tissue bank's written policies and procedures is preferred to satisfy §5.9.1 - 3 (above). In the absence of written policies, the PI may supply the IRB with a detailed written statement from the tissue bank that supplies the information requested in §5.9.1 – 3 above.

• Whether or not distribution of HBM/MRI from the tissue bank to other investigators or entities is subject to oversight by an IRB or similar review body.

• Whether or not the Source Individual can withdraw consent to research use of his/her HBM/MRI at any time, and the mechanism by which the Source Individual may affect withdrawal of such consent.

*NOTE:* The mechanism used to withdraw consent to research use of HBM/MRI should not be limited to written communication. The following example is usually adequate: “You may withdraw your consent to allow the use of your banked tissue at any time by calling Dr. ________________, the Principal Investigator, at xxx-xxx-xxxx or by making your request in writing and sending it to Dr. ________________ at Street Address; City, State, Zip Code.

• Whether there are any circumstances under which the tissue bank or individuals or entities to whom the tissue bank distributes HBM/MRI might seek to contact the Source Individual.

• Whether there exists a potential that the HBM may be subjected to genetic testing or used to create a cell line.

• Whether there exists a potential that the HBM may be used in the development of commercial products and whether or not the Source Individual may share in any financial profit

• Whether the tissue bank proposes to pay money or other remuneration to Tufts MC, Tufts University, or any member of the research team in connection with the collection or use of the HBM/MRI. If so, the nature and purpose of the remuneration must be described.

• Whether the results of any research performed on the HBM/MRI will be conveyed to the Source Individual, or his or her primary or research physician, or placed in the Source Individual’s medical records.

### 5.12.6 Policy for IRB Review

The IRB will apply the following criteria when reviewing the proposed collection of HBM and, when indicated, associated MRI (“HBM/MRI”) for transfer to a tissue bank.

When a proposed research study involves tissue banking that is not a required component of the clinical trial (the “primary research or underlying clinical trial”) the collection, transfer, and storage of HBM/MRI for future research cannot be a condition for the subject’s participation in the primary research or underlying clinical trial, or any clinical trial.

If the proposed collection of HBM/MRI for tissue banking is a component of a research protocol (the “primary research or underlying clinical trial”) whose primary purpose is not the collection, transfer, and storage of HBM/MRI for future research, the use of a separate informed consent form (ICF) to allow the
research subject to consent to the collection, transfer, and subsequent storage of HBM/MRI is recommended. This separate optional tissue banking consent form must meet all of the requirements for informed consent stated in 45 CFR 46.116.

If the primary purpose of the research protocol is to establish a tissue bank or specifically to collect HBM to be stored in a tissue bank, a separate ICF is not required. The protocol’s ICF will, by default, address tissue banking to the extent described in this policy.

The collection, transfer, or subsequent use of the HBM/MRI must not compromise the medical care or safety of the Source Individual.

In situations in which the IRB determines that there is a potential for compromise of care or safety, the IRB may impose conditions to eliminate or minimize this potential.

If, for example, the proposed research involves HBM that are “left over” after performance of diagnostic tests on a surgically removed tumor, the IRB may guard against removal of more than the usual amount of tissue by requiring that the surgeon not know if the subject has consented to the research use of any surplus materials.

The IRB may approve proposed research that involves the collection and transfer of unidentifiable HBM/MRI to a tissue bank, provided:

- The protocol and any additional descriptive materials (protocol addenda; site-specific amendments) include the information specified above in §5 (IRB Information Requirements);
- Informed consent will be obtained in accordance with the policies in §7 (Informed Consent Form Policy);
- If the tissue bank plans to distribute HBM/MRI to other investigators, the tissue bank must provide the IRB with its written policies that govern:
  - The types of investigators or entities to whom the HBM/MRI may be distributed, and
  - The types of research for which the HBM/MRI may be used, and
  - The tissue bank’s practices regarding IRB and/or ethics committee review of research for which the tissue bank may release HBM/MRI, and
  - The measures taken to abide by HIPAA regulations to protect the confidentiality of the Source Individual.

**NOTE:** A copy of the tissue bank's written policies and procedures is preferred to satisfy §6.6.3.1 - 4 (above). In the absence of written policies, the PI may supply the IRB with a detailed written statement from the tissue bank that supplies the information requested in §6.6.3.1 - 4 above.

The IRB may approve proposed research that involves the collection, transfer, and storage of identifiable HBM/MRI in a tissue bank, provided the protocol or site-specific protocol appendix include the information specified above in §5 (IRB Information Requirements), and

The HBM/MRI are coded, and

The key to the code remains within the exclusive possession and control of a designated individual or individuals at Tufts MC/Tufts University, and

An agreement is created between the PI and the tissue bank that the key to the code will never be shared with the tissue bank, secondary recipients of the HBM, or with anyone else except pursuant to IRB
approval or as necessary for an audit to ensure that written informed consent was obtained;

**NOTE:** Sometimes a tissue bank may send HBM/MRI to the PI who initially collected and submitted the HBM/MRI to the tissue bank. To protect against loss of confidentiality in a situation in which the investigator who initially collects HBM/MRI for the tissue bank subsequently receives a distribution of those same materials from the tissue bank, the IRB may consider requesting that investigators, co-investigators, research coordinators and other research team members not be the custodian of the key to the code. The IRB must rely on the PI to recognize the potential for this occurrence and to appoint a custodian of the key who is not a member of the research team.

The protocol or site-specific protocol appendix identifies a secure location in which the designated individual(s) will keep the key to the code and identifies the procedures to assure its privacy; Written informed consent will be obtained in accordance with the policy in the Informed Consent Form Policy section below);

The Source Individual is able to withdraw consent at any time to the future use of HBM/MRI that have been transferred to the tissue bank, except where it is impossible to achieve the withdrawal because:

- The tissue bank has already distributed the HBM/MRI to other investigators/entities, or
- The HBM has been completely exhausted; or
- The code is no longer available.
- The research protocol or site-specific protocol appendix identifies whether or not the results of research performed on HBM/MRI that have been transferred to the tissue bank will be communicated to the Source Individual, to the individual’s attending (research) physician, to the individual’s primary physician, or placed in the individual’s medical record.

If results are to be transferred to any of the above-cited individuals or to the medical record, the PI must provide a justification in the protocol (or in a site-specific protocol addendum) for such transfer and the planned transfer must be approved by the IRB. If approved, the subject must be informed in the ICF of the proposed transfer of research results and the potential benefits and risks of the information to be transferred.

In specific circumstances, the IRB may approve proposed research that involves the collection and transfer of HBM/MRI that have not been stripped of all HIPAA-defined identifiers, provided requirements 5.11, 5.12, and 5.16 of the immediately preceding § are met; and

The protocol and associated materials are well designed as determined by the Tufts MC and TUHS SRC; and the intended research uses of the HBM/MRI cannot reasonably be carried out if all identifiers are removed; and the PI names or describes the specific identifiers that are necessary to the proposed research uses in:

- The protocol or in the site-specific appendix, and
- The ICF.

All other identifiers must be removed prior to transfer of HBM/MRI to the tissue bank. The privacy risks to the Source Individual are reasonable in relation to the importance of the knowledge that may be developed through the research uses of the HBM/MRI. The tissue bank will only allow use of the banked HBM/MRI pursuant to an IRB-approved research protocol.

**NOTE:** If the tissue bank is a covered entity under HIPAA, the PI or the tissue bank must provide certification to the IRB that any subsequent release of HIPAA-identified materials from the tissue bank to researchers will be in accordance with the requirements of HIPAA.
IRB approval of the provision of HBM-associated MRI to the tissue bank may include MRI that is available at the time the initial HBM is transferred to the tissue bank or may include MRI generated subsequent to that date, or both.

If the PI wishes to provide MRI to the tissue bank subsequent to the original submission, the PI must provide the IRB with justification as to why the provision of additional MRI is necessary along with the frequency and duration of such subsequent submissions. The IRB must then determine whether or not the proposed multiple submissions of MRI is within the scope of the proposed research. See also: Informed Consent Form Policies below.

No HIV-test information may be disclosed to a tissue bank unless the Source Individual has provided the specific consent for disclosure of such information that is required under Massachusetts law.

The IRB may require the tissue bank to provide written assurance that it will not make any attempt, through use of other databases or other means, to ascertain the identity of the Source Individual, and may require the tissue bank to agree to return to Tufts MC/Tufts University any HBM/MRI that are inadvertently transferred to the tissue bank with identifiers.

The IRB may, with respect to specific proposed research, impose any other conditions that it deems necessary or advisable for the protection of human subjects. For example, if the written policies of the tissue bank do not describe with sufficient specificity the research purposes for which the HBM may be used, the IRB may condition approval upon written assurance that the tissue bank is subject to oversight by an IRB, ethics committee, or similar body, and that the recipient investigators are bound to abide by the conditions specified by that IRB.

The IRB may submit to the relevant legal office for its review any research protocol that involves the transfer of money or other remuneration from the tissue bank to Tufts MC, Tufts University, or the PI in connection with the use of the HBM. The IRB will not consider the research protocol for final approval until the IRB receives written notification from the legal office that all legal issues, if any, have been satisfactorily resolved.

**5.12.7 Informed Consent Policies for Tissue Banking**

The following information must be included in the ICF:

- A description of the HBM to be collected.
- A description of the manner in which the HBM will be collected. In particular, whether the involvement of the tissue bank will necessitate the performance of procedures in addition to, or taking of materials in a greater volume than, that which would otherwise be done as part of the underlying clinical trial.
  
  If the collection of HBM involves the performance of procedures in addition to those that would be performed as part of the underlying clinical trial, or involves the collection of materials in a greater volume than would be collected as part of the underlying clinical trial, an explanation of the associated risks, if any.

- If associated MRI will also be collected, a detailed description of the specific information involved as well as the frequency of its collection and transfer to the tissue bank.

- A statement that the Source Individual’s agreement to collection of HBM/MRI for transfer to a tissue bank is not a condition for enrollment in any research trial or for future care or treatment at Tufts MC or Tufts University.
A description of the measures that will be taken to guard against loss of confidentiality.

A description of (a) the types of investigators/entities to whom the HBM/MRI may be distributed, and (b) the purposes for which the HBM/MRI may be used. The ICF is to describe the intended purposes for the future use of the materials with as much specificity as possible.

If the HBM/MRI will be coded, a statement that the Source Individual is able to withdraw consent at any time to future use of the HBM/MRI, except where it is impossible to achieve the withdrawal because the tissue bank has already distributed the HBM/MRI, the HBM has been completely exhausted, or the code is no longer available.

If the HBM/MRI will be coded, a statement indicating that the PI is the person to contact if the source individual wishes to withdraw consent to the future use of the HBM/MRI.

NOTE: the mechanism used to withdraw consent to the research use of HBM/MRI should not be limited to written communication. The following example is usually adequate: “You may withdraw your consent to allow the use of your banked tissue at any time by calling Dr. ________________, the Principal Investigator, at xxx-xxx-xxxx or by making your request in writing and sending it to Dr. _________________ at Street Address; City, State, Zip Code.

A statement that a risk of participation includes the possible loss of confidentiality and, if genetic testing is part of the protocol, a statement to the effect that the results of genetic tests, if inadvertently disclosed, could negatively affect access to insurance or employment, or could have an impact upon family or social relationships.

A statement that the Source Individual will not be contacted by the tissue bank or by secondary recipients of HBM/MRI distributed by the tissue bank. If the IRB allows such contact, the ICF must state the circumstances under which such contact may occur.

A statement, if applicable, that the HBM will or may be used in the development of commercial products, including the development of cell lines and whether the Source Individual will receive any benefit or monetary gain from such development.

A statement addressing whether or not the Source Individual will receive any direct benefit from participation in the tissue banking component of the research protocol.

A statement describing whether or not, once the Source Individual’s HBM have been transferred to the tissue bank, the results of research performed on those materials will be communicated to the Source Individual or to the individual’s attending (or research) physician, the individual’s primary physician, or placed in the individual’s medical record.

If research results are to be communicated to the Source Individual’s attending (research) physician, the Source Individual’s primary physician, or placed in the Source Individual’s medical records, the potential benefits and risks of such transfer and placement of information must be stated in the ICF.

An explanation, if applicable, that Tufts MC, Tufts University, or a member of the research team will receive money or other remuneration from the tissue bank for the collection or use of the HBM. No explanation is necessary if the remuneration is intended solely as reimbursement for the direct costs of the collection of the materials and transfer to the tissue bank.

If the IRB approves a research protocol that allows identifiable MRI to accompany the HBM supplied to a tissue bank, the ICF must include each of the following additional elements:

- An expiration date or expiration event for the potential research to be performed on the Source Individual’s HBM/MRI;
A statement that once MRI is disclosed to the tissue bank, subsequent release of MRI by the tissue bank may not be protected by the federal privacy rule;

- A statement that the Source Individual may inspect or copy the medical record information to be disclosed to the tissue bank; and

- A statement describing the particular identifier(s) that will be disclosed to the tissue bank (for example, date of birth, zip code, etc.).

If it is anticipated that the Source Individual’s MRI will be supplied to the tissue bank on an ongoing basis, the ICF must:

1. Explicitly disclose that MRI will continue to be collected from future medical records on an ongoing basis and transferred to the tissue bank; and

2. State any risks associated with supplying the Source Individual’s MRI to the tissue bank on an ongoing basis; and

3. Describe the specific information to be disclosed, the frequency of its disclosure, and the time period during which it will be disclosed; and

4. State that the ongoing disclosure of medical record information will terminate once all research on the individual’s HBM has been completed; and

5. State that the individual can, at any time, revoke permission for the ongoing collection of information from his or her medical records and include the mechanism for doing so.

### 5.12.8 Identifiers for Tissue Banking

An **Identifier** is any one of the following types of information about the individual (or the relatives, employers, or household members of the individual) from whom the HBM are collected:

- Name
- All 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 if, according to the current publicly available data from the Bureau of the Census:
  - The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
  - The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
- All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of date (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
• Web Universal Resource Locators (URLs)
• Internet Protocol (IP) address numbers
• Biometric identifiers, including finger and voice prints
• Full face photographic images and any comparable images
• Any other unique identifying characteristic.

5.14 EDUCATION REQUIREMENTS

5.14.1 Research Community

PIs and the institutions share responsibility for ensuring that the PI, co-investigators, and all other personnel (referred to as the "research team members") involved in the conduct of human subjects research fulfill basic educational requirements in compliance with all applicable laws, regulations and institutional policies (see http://viceprovost.tufts.edu/HSCIRB/).

The institutions define “research team members” as persons, who have direct contact with subjects, contribute to the research in a substantive way; have contact with subjects’ identifiable data or biological samples (e.g., tissue, blood, urine, plasma, saliva), or use subjects’ personal information.

For example, a nurse who ordinarily works in the clinical context but becomes involved in a research protocol obtaining informed consents and drawing bloods for research would be considered a research team member. A lab technician, narrowly involved on the project, working only with de-identified data would not be a research team member. On the other hand, a biostatistician working with identifiable data would be considered a member of the research team.

Please Note: Because of the variability in research situations, it is impossible for the institutions to define precisely every category of employee who could be considered to be a member of a research team. Some interpretation by PIs will be needed. The PI is expected to make a good faith effort to meet the spirit of this requirement by assuring that all members of the research team receive education appropriate to their role in the project.

88 The information provided here is only intended to assist with the definition of the “research team member,” and is not intended to address issues associated with mentorship or authorship.

89 There may be some exceptions. For example, there may be individuals whose primary contact with the subject is in the context of clinical care but who might play a minimal role in the research. An example of this would be a nurse or phlebotomist drawing blood for a clinical purpose and taking an extra sample at the same time for someone else’s research project. In this case, provided that someone other than the nurse or phlebotomist administered informed consent and that the nurse/phlebotomist would not be playing any further role in the research, s/he would not be considered a research team member, and no educational requirement would apply.

90 Employees that may compose your research team could include research coordinators, nurses, recruiters, dieticians, laboratory technicians, data entry/analysis persons etc., that need to meet the educational requirements outlined by the institutions.
For additional information in determining who constitutes a research team member and determining who needs to fulfill the educational requirements, investigators are directed to OHRP guidance on engagement in research.  

Continuing education for research team members is required on an annual basis. The current mandatory research education requirements for researchers are appended to this manual. The Institutional Officials, in consultation with the IRB Chair and the Manager of IRB Operations, shall determine requirements and resources. Individuals are to retain their certificate of completion. PIs are required to retain a copy of education certificates for all research team members: These documents are subject to audit.

The institutions shall also periodically offer and/or sponsor education sessions for the research community. The institutions encourage investigators and research team members to avail themselves of institutional and local resources for additional education opportunities. The institutions have committed space and resources for an IRB library of reference materials, which are available to all research team members.

5.14.2 IRB Leadership, Members, Office Staff

The institutions shall provide opportunities to the IRB Chair, Vice-Chairs, members, and office staff for continuing education. Opportunities include education sessions, seminars, conferences, etc. Funds and time to attend education sessions are dispersed as available by the institutional officials and is encouraged. The IRB Chair, Vice-Chair, and members also complete research education requirements annually. The current mandatory research education requirements for IRB members are appended to this manual. Texts such as Bankert and Amdur’s Institutional Review Board Management and Function are available for personal use, and a library of reference materials is available in the IRB office.

5.15 Documentation Requirements for Unaffiliated Investigators

Applications for studies involving unaffiliated investigators are to include the following documents:

Unaffiliated investigators must comply with the Tufts MC/TUHS human subjects protection education requirements or supply the completion certificate of the education program approved at his or her home institution, along with verification of the institution’s education program. If the unaffiliated investigator has not met the Tufts MC/TUHS requirements, the IRB Chair, Vice-Chair, or designee will review their submitted documents for equivalence. If not deemed equivalent, the unaffiliated investigator will need to complete the Tufts MC/TUHS requirements.

In addition, an unaffiliated investigator must supply the current IRB approval of his or her home institution, if applicable.

Investigators who are not affiliated with Tufts MC/TUHS may engage in on-site human research activities only if a member of the professional or medical staff agrees to be his or her institutional sponsor. The institutional sponsor must provide a letter of support stating that he or she will oversee the on-site activities and providing a description of his or her role in the conduct of the study. The institutional sponsor is responsible for ensuring that the unaffiliated investigator complies with applicable institutional training and credentialing requirements.

91 OPRR Guidance, Engagement of Institutions in Research, 16 October 2008
5.16 Health Insurance Portability and Accountability Act (HIPAA)

Please refer to the HIPAA documents on the IRB website. The HIPAA Privacy Office maintains specific policies addressing HIPAA in the research context. As of 04/01/12 all new research studies submitted for initial review will contain the HIPAA research authorization language in the ICF. All other studies will have the option of either continuing with a separate HIPAA RAF and ICF or converting to one combined document. RAFs may be reviewed by the IRB during a study review process as a courtesy; however, RAFs are not approved by the IRB.

5.17 Research Policy on Case Reports

Case reports submitted for publication do not strictly meet the criteria of research. Although a case report (defined as a retrospective analysis of 1, 2, or three (3) clinical cases) may be illustrative, it does not meet the Federal Policy for the Protection of Human Subjects definition of Research, which requires an investigation that contributes to generalizable knowledge about a disease or condition. Instead, a case report is intended to develop information to be shared for medical or educational purposes.

The institution’s policy, therefore, is that a case report is not research that must be approved by the IRB. If an author wants to have a project assessed by the IRB to determine whether it meets the institution’s definition of a case report the author may contact the IRB.

Although there is no requirement of IRB approval for a case report, the HIPAA Privacy Rule restricts how protected health information (individually identifiable health information) may be used and disclosed. HIPAA requires written authorization for certain uses and disclosures of an individual’s protected health information, including publication of a single case report.

An author may be exempted from obtaining a signed authorization from the patient discussed in the case report if certain identifiers are removed from the case report prior to disclosure (i.e., before the case report is submitted to a journal). The removal should be done by a member of the Tufts MC/Tufts University, as applicable, workforce. It is the responsibility of the author to ensure compliance with patient privacy, institutional rules, and federal regulations. It is also the responsibility of the author to ensure that (i) no photos or illustrations that contain identifiable features are included the case report (e.g. pictures of a patient’s face or tattoos should not be included or the identifying information should not be visible) and (ii) the case(s) described in the report are not so unique or unusual that it might be possible for others to identify the patients in the case reports.

If an author wants to publish a case report that is not completely de-identified pursuant to the standards set forth in HIPAA or if there is any concern that a patient could be identified or likewise could identify themselves or a family member (for example, because the condition or diagnosis is distinct or identifiable features appear in photographs) the institutional privacy officer or his/her designee should be consulted and explicit authorization from the patient must be sought for the use of identifiable information. If a patient is deceased, authorization for the use of identifiable patient information must be obtained from the personal representative of the patient’s estate.

92 [http://viceprovost.tufts.edu/HSCIRB/](http://viceprovost.tufts.edu/HSCIRB/)

93 An analysis of more than 3 clinical cases does meet the definition of research that must receive IRB approval before commencing. These cases also require the authorization of a subject that meets the requirements set forth in HIPAA.
### 6 Other

#### 6.1 Documents and Forms Required to Initiate Review

Submission of the original following IRB forms, whether for expedited or convened IRB review, initiates application for IRB review:

<table>
<thead>
<tr>
<th>Checklist</th>
<th>A resource for investigators; a guide about required documents for research proposals. Submission to the IRB is not required.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form I</td>
<td>Required for all initial submissions, except requests for exemption. Form I must be signed by the PI and the relevant Department Chair, Division Chief, or Dean or approved designee. A PI who is also the Department Chair/Division Chief may sign for him/herself on Form I.</td>
</tr>
<tr>
<td>Site-Specific Appendix</td>
<td>Required for all industry-sponsored studies when the sponsor’s protocol cannot be tailored to include details about how the study will be executed at Tufts MC/TUHS, e.g., details of consent process, record storage, location of procedures.</td>
</tr>
<tr>
<td>Form II</td>
<td>Required for research proposals utilizing approved or investigational drugs, biologics, substances, or nutrients as part of the research. If an investigational drug is used, Form II must specify the Investigational New Drug (IND) number assigned by the FDA. All requisite supporting documentation must be provided.</td>
</tr>
<tr>
<td>Form III</td>
<td>Required for all research proposals involving devices as part of the research. Form III must specify the Investigational Device Exemption (IDE) number assigned by the FDA, unless the PI submits information that would justify classification of the device as a non-significant risk device. Written information about the device, such as the user manual, must be provided.</td>
</tr>
<tr>
<td>Form IV</td>
<td>Required when subjects will be exposed to radiation for research purposes only. The Radiation Safety Officer must review and approve the research-related radiation exposure, and indicate approval by signing Form IV. A signed Form IV is required prior to IRB approval. Studies that involve research-related ionizing radiation exposure are not eligible for expedited review.</td>
</tr>
<tr>
<td>Form VI</td>
<td>Application for Specimen/Tissue Banking An independent optional tissue banking ICF should accompany the submission.</td>
</tr>
<tr>
<td>Form VII</td>
<td>For a medical record/chart review/clinical database study. Form VII is designed to satisfy IRB and HIPAA issues in one document. Answered completely, a Form I, protocol, and HIPAA waiver of research authorization are not required.</td>
</tr>
<tr>
<td>Form VIII</td>
<td>Required for WIRB submissions.</td>
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</tbody>
</table>
The standard IRB forms are posted on the IRB website. The documents are appended to this manual for reference regarding the specific information collected on each form. They are updated and revised periodically, as needed.

A completed application for initial review consists of the original of each of the following materials; electronic copies of the documents will also be requested:

- Forms I — IV and VI, as required, including required supporting documentation
- Protocol and a site-specific appendix, as indicated.
- ICF(s)
- Grant application, letters of support, etc., as required
- All materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaires, survey instruments, diaries, subject information pamphlets, instruction sheet(s), recruitment materials (e.g., advertisements flyers, website postings, e-mail announcements), and contact letters, if applicable.
- HIPAA documentation.
- Guidelines of Tissue Bank, if applicable.
- Tissue banking-specific ICF, if applicable.

Note: the PI is instructed to retain a copy of all items submitted to the IRB.

All original IRB forms and correspondence submitted to the IRB office are to be signed and dated by the PI. Signature stamps and electronic signatures may not be accepted. Under certain circumstance a Co-Investigator may sign the submission documents instead of the PI. The Co-Investigator may sign IRB forms and official correspondence only if the PI is unavailable (e.g. leave of absence, illness, etc.). Under such circumstances, a letter stating the circumstances, signed by the Co-Investigator, should be sent to the IRB office for the study file. A Co-Investigator should contact the IRB office for guidance in such an event.

All documents submitted to the IRB are to be free of correction fluid (“white-out”) and informal notes (“post-its”).

Upon receipt of an application for review, the IRB office will pre-review the application for completeness. The PI or research team may be contacted if any of the required materials is missing or if the applicable forms have not been completed accurately or in their entirety.

The materials and information requested by the IRB are necessary to enable a thorough review of the research proposal in conformity with applicable laws, regulations, and federal guidance.

94 [http://viceprovost.tufts.edu/HSCIRB/]
6.2 Documents for Initial Review – IRB members

The primary reviewer of an initially submitted study will have a copy of the following documents prior to the convened IRB meeting:

- Protocol and a site-specific appendix, if indicated
- ICF(s)
- Required applicable IRB Forms and supporting documentation (i.e., Forms I-IV, VI, site-specific appendix, as applicable)
- Investigator’s Brochure, device information, etc., if applicable
- A copy of the current FDA-approved package insert for approved drugs, scientific articles, MSDS sheets, etc., if applicable, device user manual/operating manual, etc., as applicable
- All materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaires, survey instruments, advertisements and letters, etc., as necessary and if applicable.
- Recruitment materials (letters, advertisements, postings, e-mail announcements, etc.), if applicable.
- Guidelines of Tissue Bank, if applicable.
- Tissue banking-specific ICF, if applicable.
- Any instruction sheet(s), informational sheet(s), contact letter(s), as required.
- HIPAA documentation, as applicable.

6.3 Documents Required for Continuing Review

A completed application for continuing review consists of the original of each of the following materials; electronic copies of the documents will also be requested:

- Form V
- Forms II–IV and VI, as applicable.
- ICF(s)
- Grant application, letters of support, etc., as required
- All materials provided to subjects including, but not limited to, telephone scripts, interview text, questionnaires, survey instruments, advertisements and cover letters, if applicable.
- Recruitment materials (letters, advertisements, postings, e-mail announcements, etc.), if applicable.
- HIPAA documentation, as applicable.
- Guidelines of Tissue Bank, if applicable.
Tissue banking-specific ICF, if applicable.

Any instruction sheet(s), informational sheet(s), contact letter(s), as required.

One copy of the validated ICF(s) used to enroll subjects during the past year

One copy of the current protocol and a site-specific appendix, as indicated. If the PI seeks to modify the existing protocol/site-specific appendix, s/he must submit a detailed written description of the proposed changes and a tracked and untracked copy of the revised protocol/site-specific appendix as part of the continuing review process.

DSMB report, if applicable

Summary of SAEs, if applicable

All original IRB forms and correspondence submitted to the IRB office are to be signed and dated by the PI. Signature stamps and electronic signatures may not be accepted. Under certain circumstances a Co-Investigator may sign the submission documents instead of the PI. The Co-Investigator may sign IRB forms and official correspondence only if the PI is unavailable (e.g. leave of absence, illness, etc.). Under such circumstances, a letter stating the circumstances, signed by the Co-Investigator, is to be sent with the submission. A Co-Investigator should contact the IRB office for guidance in such an event.

All documents submitted to the IRB should be free of correction fluid (“white-out”) and informal notes (“post-its”).

Upon receipt of an application for review, the IRB office will pre-review the application for completeness. The PI or research team may be contacted if any of the required materials is missing or if the applicable forms have not been completed accurately or in their entirety.

The materials and information requested by the IRB are necessary to enable a thorough review of the research proposal in conformity with applicable laws, regulations, and federal guidance.

6.4 Documents for Continuing Review – IRB Members

Each IRB member who will attend the convened IRB meeting will receive a copy of the following minimum information prior to a study being presented to the convened IRB for continuing review:

- Form V
- ICFs
- Protocol and a site-specific appendix, as indicated.

6.5 Information Required for IRB Notification

If present from the prior month, each IRB member will receive notification of the following events in a monthly compilation:

- Exempt status certifications
- Expedited Initial Review Approval
6.6 Proposed Changes to Protocol and/or ICF: Change to a Protocol Previously Approved

Prior to any meeting at which a proposed change to the protocol/site-specific appendix or informed consent form(s) is considered, the PI is to submit:

- PI’s request for amendment
- Detailed description of proposed change(s)
- Explanation of the rationale for the change(s)
- Revised protocol/site-specific appendix and validated ICF(s), as applicable. One copy of both the tracked and untracked documents including an updated version date or number. The IRB prefers that the tracked changes document be in Microsoft Word track changes format with both insertions and deletions noted. Only changes since the last accepted version should be tracked.

In addition to the above, the primary reviewer should have a copy of the following:

- Protocol and a site-specific appendix, as indicated.
- ICF(s)
- Any additional supporting information pertinent to the proposed change(s) such as information supplied by the study sponsor, articles published in the primary literature, etc.

A complete copy of the IRB file for all studies on an agenda is available in the IRB office for review by IRB members prior to a meeting. A complete copy of the IRB file for each study placed on an agenda for initial review shall be available to the IRB members.

6.7 Changes and Modifications of Policies and Procedures

6.7.1 Operations Manual

Appendices, including new or revised policies, may be added to this manual at any time. The manual will be reviewed and appended policies incorporated at appropriate intervals.
6.7.2 IRB Policy on Approval of New Policies (version dated 01/19/07, accepted by Executive Committee 01/23/07)

IRB policy revision and creation will occur at regular intervals, on an as needed basis.

If a revised or new policy does not affect the function of the convened IRB or its decision-making, a drafted policy will be circulated for review and discussion at an IRB Executive Committee meeting. Based on discussion by the Executive Committee members, revisions may be made. Policy decisions of the Executive Committee will be reached by consensus, not by vote. When the final version of a policy is accepted, the date of acceptance will be documented in the policy. Such new or revised policies will be announced at the convened IRB meetings as relevant.

Policies that affect the function of the convened IRB or its decision-making process will be drafted by the IRB Executive Committee and will be voted on by the convened IRB. The vote will be recorded.

6.8 SUMMARY OF REVISIONS

<table>
<thead>
<tr>
<th>Issue</th>
<th>Section of document revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Policy on Approval of New Policies</td>
<td>6.7.2</td>
</tr>
<tr>
<td>Policies of the Executive Committee</td>
<td>3.1.4.1</td>
</tr>
<tr>
<td>Guidelines for the Management of Dental Distance Education Protocols</td>
<td>5.5</td>
</tr>
<tr>
<td>Tufts-New England Medical Center and Tufts-NEMC changed to Tufts Medical Center (Tufts MC) throughout document.</td>
<td></td>
</tr>
<tr>
<td>Website/url updates</td>
<td></td>
</tr>
<tr>
<td>o IRB office website url updated on various pages</td>
<td></td>
</tr>
<tr>
<td>o Section 4.1, Not Human Subject Research (page 31), updated to reflect most recent guidance from OHRP.</td>
<td></td>
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<tr>
<td>o Section 3.2, Scope of IRB Review Responsibility (page 12), updated to reflect most recent guidance from OHRP.</td>
<td></td>
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<tr>
<td>Various updates and revisions</td>
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</tr>
<tr>
<td>1. Summary of Revisions: Removed page numbers of previously revised sections as repagination has resulted from subsequent revisions</td>
<td>6.8</td>
</tr>
<tr>
<td>2. Revisions to Translation of Study Documents</td>
<td>5.2.1</td>
</tr>
</tbody>
</table>
a. Added “Documents prepared by professional translation services will be considered based on the quality assurance procedures utilized by the service. The Chair or Vice Chair reviewing these procedures will determine if they meet the institutional standards.”

3. Unanticipated problem and Adverse Event Reporting policy 4.10
   Policy version 17 August 2009
   Accepted by the IRB Executive Committee 13 August 2009
   Accepted by IRB-RED 13 October 2009
   Accepted by IRB-BLUE 29 October 2009
   Effective 01 April 2010

4. IRB Review of Proposed Research Involving Tissue Banking 5.13
   Policy version 07 August 2009
   Accepted by the IRB Executive Committee 13 August 2009
   Accepted by IRB-RED 08 September 2009
   Accepted by IRB-BLUE 24 September 2009
   Effective 01 April 2010

5. WIRB review option 3.9

6. Short form use 5.1.6

7. Various administrative, non-safety related, revisions made throughout document, e.g., copies of research education certificates of completion not to be submitted to IRB office, PI is to retain copies for all members of the research team; revised the number of copies required for submission; included electronic (wiki) distribution of agenda to IRB members

8. Updated links, footnotes, and references throughout document.
   Version dated 19 November 2010
   Accepted by the IRB Executive Committee 19 November 2010

WIRB updates
- Added phase IV and minor updates to process. 3.9
- IRB Administrative Fee 5.9
  - Updates
  Version dated 26 May 2011
  Accepted by the IRB Executive Committee 27 May 2011

Various updates and revisions
- CIRB procedures added 3.9
- Updated SAE language and forms; corrected use of possibly/probably 4.10
- Clarified language related to PI record retention 4.11.2.4
- Form II revised, Form II instruction sheet created, and 2011 Continuing Education announcements incorporated; see appended forms
  Version dated 08 August 2011
  Accepted by the IRB Executive Committee 11 August 2011

Various updates and revisions
- WIRB (addition of phase II) 3.9
- HIPAA (Reference to combined or separate ICF and RAF) 5.16
- Policy on Case Reports 5.17
- Eliminate copies from submissions (new, CR) 6.3
- 2012 IRB member and research team continuing education
- Forms (eliminated need for additional copies, included request for electronic documents, revision for ICF/RAF combination document, added 2012 education, Blood Borne Pathogen language revised)
Various updates and revisions

- Continuing review sections updated to reflect OHRP and FDA guidance documents on continuing review (e.g., fixed anniversary dates) 4.2.8.2, 4.3
- Typographical errors corrected various locations

Version dated 09 May 2012
Accepted by the IRB Executive Committee 10 May 2012

Various updates and revisions

- Revised CIRB language to reflect the new Independent Model 3.9.1
- Eliminated CTRC as having access to IRB study files 3.6
- Minor editing various locations

Version dated 06 November 2013
Accepted by the IRB Executive Committee 07 November 2013

Various updates and revisions

- Simplified WIRB submission information 3.8
- Revisions to reflect WIRB-Copernicus Single Review Solution information 3.8

Version dated 01 May 2014
Accepted by the IRB Executive Committee 15 May 2014