

Boston University/ Boston Medical Center IRB Policies and Procedures

Table of Contents

I. Introduction	3
Ethical Principles	3
II. Scope of Authority	3
Scope of Authority Defined	3
Statutory Basis for IRB Authority / Regulatory Agencies	4
Organizational Structure	5
Multi-Institutional Research.....	5
International Research.....	6
III. Structure of the BU/BMC Institutional Review Board	6
Panels	6
IRB Board members.....	7
Leadership	8
Training of IRB Chairs, Vice-Chairs, and members	11
Compensation of IRB Members	11
Liability Coverage for IRB Members	11
Use of Consultants.....	12
IRB Member Conflict of Interest Policy	12
IRB Office Staff: Analysts, Coordinators, IT Applications Specialist and Secretarial support and resources	12
IV. IRB Office staff	13
Responsibilities	13
Administrator	14
IRB Analysts, Coordinators and Administrative Staff	14
IRB Records.....	15
V. IRB Meetings	17
Location.....	17
Scheduling of Meetings.....	17
Visitors	18
Quorum / Voting Procedures:.....	18
Minutes and Agendas	19
Notification of IRB Actions to the Institutional Official	20
Communication with Investigators Conveying the Outcome of IRB Meetings	20
VI. Principal Investigators, Co-investigators and Other Research Personnel	20
Qualifications to Perform Human Research	20
Requirements for Principal Investigators	21
Communication between IRB and Investigators	22
Training of Investigators.....	22
Investigator Conflict of Interest.....	23
PI Responsibilities when Conducting Research at BU/BMC.....	23
Continuing Review	23
Reporting of an Unanticipated Problem (UP), Adverse Event (AE) and Serious Adverse Event (SAE)	25
Definitions	25
Amendments and Modifications to Protocols	27
Protocol Deviations	27
Final Report	28
Maintaining Research Records	28
Transferring a Protocol to another Investigator.....	28
VII. Research Protocols	28
Preparing a Protocol for Submission to the IRB.....	28

Protocol Submission	29
Signatures Required	31
VIII. Informed Consent	32
Federal Regulations regarding Informed Consent	32
Elements of Informed Consent	32
Review of Informed Consent	33
Informed Consent Categories	34
Children	36
Prisoners	37
Pregnant Women, Fetuses, or Neonates	37
Decisionally Impaired Persons	39
Students, Trainees (e.g.; medical residents), and Employees	39
X. IRB Procedures for the Review of Protocols and Amendments	40
Conducting Initial and Continuing Review	40
Types of Review	41
(Convened) Full Board Review	41
Expedited Review	42
Exempt From Review	42
Review Decisions	45
Determining Studies That Require Review More Often Than Annually	46
Notification of Investigators	47
Investigator's Right to Appeal	47
XI. Compliance Oversight of Research	47
Quality Assurance Audits of Research	47
Non-Compliance	49
Serious or Continuing Noncompliance	49
Suspension or Termination of IRB Approval	50
XII. Special Topics	50
Investigational New Drug (IND)	51
Investigational Device Exemption (IDE)	52
Emergency Use Notification and Reporting	52
Humanitarian Device Exemptions	53
XIII. Appendix	
Guidelines for Enrolling Students as Research Subjects	

I. Introduction

Boston University (BU) and Boston Medical Center (BMC) establish these policies and procedures to govern the conduct of research involving human subjects and all other activities which even in part involve such research, regardless of sponsorship.

The BU/BMC Institutional Review Board (BU/BMC IRB) was created first through the merger of the Boston City Hospital Human Studies Committee and Boston University Medical Center Institutional Review Board in 1996 and then with the addition of the Boston University IRB in 2010. The constituent members have designated the BU/BMC IRB as their IRB of record under a Federalwide Assurance (00000301)...

These policies also apply to research at entities that have designated the BU/BMC IRB as their IRB of record under a Federalwide Assurance (FWA) granted by OHRP (Office of Human Research Protections).

The role of the IRB in the institution is to protect the rights and welfare of human subjects of research and to assure that clinical research is conducted according to corresponding federal regulations, state law, and IRB policies.

Ethical Principles

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and published in 1979 delineates the ethical principles for the conduct of human research upon which the United States federal regulations are based.

The BU/BMC IRB applies the Belmont Principles to its deliberations and decision-making in its goal to protect the rights and welfare of human subjects of research, while applying federal regulations and state laws to human research.

Those principles are:

Respect for persons involves recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

Beneficence entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

Justice requires that the benefits and burdens of research be distributed fairly.

II. Scope of Authority

Scope of Authority Defined

All research or clinical investigations involving human subjects in which BU, BMC, its faculty, staff, or its students are engaged may be subject to the authority of the IRB, regardless of funding source or other regulatory requirements.

Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge [45 CFR 46.102 (d)]

For FDA-regulated research, **clinical investigation** is defined as any experiment that involves a test

article and one or more human subjects and that is either subject to requirements for prior submission to the FDA, or the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. [21 CFR 50.3(c)]

Human subject is defined as a living individual about whom a researcher obtains data through intervention or interaction with the individual, or identifiable private information about the individual [45 CFR 46.102(f)] or an individual who is or becomes a subject (either a healthy human or a patient) in research, either as a recipient of the test article or as a control [21 CFR 50.3(g)].

The IRB has the authority to:

- a. Approve, require modifications in (to secure approval), or disapprove all human research activities.
- b. Conduct continuing review of the research not less than once a year and require progress reports from study investigators.
- c. Oversee the conduct of the research, including observation of the consent process.
- d. Place restrictions on a study,
- e. Suspend or terminate IRB approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects or any unanticipated problems involving risks to human subjects or others.

Statutory Basis for IRB Authority / Regulatory Agencies

The BU/BMC IRB is subject to regulation and inspection by all governmental regulatory agencies, including the Food and Drug Administration and the Department of Health and Human Services' Office of Human Research Protection. In addition, the laws of the Commonwealth of Massachusetts (94C) also apply.

Federal Regulatory Authority for Institutional Review Board operations and human research standards:

- Food and Drug Administration (FDA) regulations pertaining to rights and welfare of subjects participating in research involving products regulated by the FDA, including drugs, medical devices and biological products. [21 CFR Parts 50 and 56]
- Department of Health and Human Services (DHH) regulations pertaining to rights and welfare of subjects participating in research supported with federal funding. [45 CFR Part 46 (*Federal Policy for the Protection of Human Subjects*)].
- Commonwealth of Massachusetts Controlled Substances Act, General Laws, Chapter 94C, Section 8 (Research Projects and Studies) requires researchers to give evidence of compliance with federal law to the Commissioner of Public Health.

State Statutory and Regulatory Authority for Institutional Review Boards:

- Code of Massachusetts Regulations Title 105, Chapter 700.009 Implementation of M.G.L. Chapter.94C.
- Commonwealth of Massachusetts Fetal Research Law: General Laws, Chapter 112, Section 12J
- General Laws Chapter 111. Section 70G: Modified requirements for genetic testing under protocols subject to and conducted in accordance with review and approval of an IRB under 45 CFR Part 46 or 21 CFR Parts 50 and 56.

Organizational Structure

The Institutional Official (IO) is the FWA Signatory Official. The IO is a high-level institutional official who has the authority to represent the institution named in the Federalwide Assurance (FWA), as well as all the institutional components listed in the FWA. Entities that the Signatory Official is not authorized to represent may not be covered under the FWA. The intent of OHRP in requiring that the Signatory Official be a high-level individual is two-fold. First, OHRP encourages institutions to promote a culture of conscience for the ethical conduct of human subjects research at the highest level within the institution. Second, the Signatory Official should be at a level of responsibility that would allow authorization of necessary administrative or legal action should that be required. OHRP recommends that the Signatory Official not be the chair or member of any IRB designated under the FWA.

BU/BMC IRB Institutional Official (IO) is the Associate Provost of Boston University Medical Campus. The IRB reports to the Institutional Official, via the Director of the IRB, for human subjects and administrative issues. Although the IRB reports to the Institutional Official, it retains autonomy in decision-making. IRB disapprovals, restrictions, or conditions cannot be rescinded or removed except by the action of the IRB.

The IRB reports to the Institution by providing the Institutional Official (IO) with a copy of the minutes of all IRB meetings. In addition the IRB Director meets regularly with the Institutional Official. The IRB Chairs meet with the IO as needed. The IO attends the monthly IRB Executive Committee meetings.

Human research that has been approved by the IRB may be subject to further review and approval or disapproval by other BU or BMC officials or committees or by officials of entities that rely on the BU/BMC IRB. However, non-exempt human subjects research conducted under BU/BMC's FWA may only be conducted if approved by one of the IRBs listed under that FWA.

IRB Jurisdiction

The IRB reviews all research in which a BU/BMC constituent or entity relying on the BU/BMC IRB is engaged in human research. The BU/BMC IRB uses the OHRP guidance, <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>, in making determinations regarding whether or not BU/BMC is engaged in research.

Multi-Institutional Research

For research conducted concurrently at BU/BMC and at another institution, (where both institutions are determined to be engaged in that research), the BU/BMC IRB and the other institution's IRB each review and approve the full protocol and consent form(s) unless:

- there is an IRB Authorization Agreement in place between BU/BMC and the other FWA assured institution engaged in the research specifying that BU/BMC will cede IRB review to the other institution
- OR
- there is an IRB Authorization Agreement in place that allows BU/BMC's responsibility for IRB review to be ceded to another IRB listed on BU/BMC's FWA

If all subjects are to be enrolled at the "other" non-BU/BMC assured institution then the BU/BMC IRB may determine that a BU/BMC consent form does NOT have to be created. BU/BMC can waive the requirement for BU/BMC standard language or formatting elements to be included in the ICF. In such instances when BU/BMC accepts the other institution's consent form for review with the protocol, the BU/BMC IRB still reviews the consent as part of the approval process to ensure that all the required elements of consent are present and that the consent language is consistent with BU/BMC local policies and procedures and local context.

- The BU/BMC IRB reviews study protocols for research conducted at the Veterans Administration Medical Center (VAMC) when BU/BMC is engaged in the research. When all research subjects are enrolled at the VA the BU/BMC IRB does not validate the ICFs and the VA retains the oversight responsibility for any research being conducted at their facility.

For each protocol approved by the BU/BMC IRB, the BU/BMC IRB also reviews all amendments (protocol changes), Progress Reports, unanticipated problems, deviations, and protocol exceptions.

The BU/BMC IRB is responsible for the protection of the rights and welfare of human subjects in research conducted at Boston University and Boston Medical Center and other locations by BU/BMC faculty and staff who are engaged in the research. The BU/BMC IRB makes determinations regarding “engagement in research” in accordance with the OHRP guidance on engagement in research, <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html> . The BU/BMC IRB staff may determine that research is “exempt from further review by BU/BMC” because it has determined that BU/BMC is not engaged in the research.

International Research

Research conducted outside the United States under BU/BMC’s FWA must comply with the conditions of BU/BMC’s FWA and all BU/BMC IRB policies and procedures.

Each international study conducted under the BU/BMC FWA must have a BU/BMC investigator who is accountable to the BU/BMC IRB for the conduct of the research.

As part of IRB review the IRB reviews the protocol for appropriate local context. The BU/BMC IRB follows the OHRP guidance regarding local context <http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm>. The BU/BMC IRB may use local and international consultants, including IRBs from the countries where the research is being conducted to provide information regarding local context. The BU/BMC researcher is responsible for knowing and complying with any laws, regulations or policies in the host country.

Click here for BU/BMC policy regarding Local Context Review:

<http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/Word%20Doc/Local%20Context%20Review%20of%20International%20Research.doc>

III. Structure of the BU/BMC Institutional Review Board

Panels

Panels

In-house Panels

The BUMC IRB is comprised of one internal panel on the Charles River Campus (which primarily reviews social and behavioral research) and three internal panels (Panel Blue, Panel Green, and Panel Purple) on the medical campus which review biomedical and social/behavioral research.

Commercial and Central IRBs

BU/BMC has entered in to an Authorization Agreement with Western IRB (WIRB), a commercial IRB to review certain, multi-center, industry-sponsored, industry-initiated protocols. The BU/BMC IRB may also rely on facilitated reviews provided by central IRBs including the NCI and the CDC central IRBs (CIRBs). In each instance the BUMC IRB has a formal IRB Authorization Agreement in place with these IRBs to allow BUMC to cede IRB review to them. There are SOPs governing how these reviews are conducted and all of these IRBs are listed on the BU/BMC’s FWA. Investigators are informed about the requirements for submission to external IRBs through information posted on the BU/BMC IRB website www.bumc.bu.edu/irb.

IRB Authorization Agreements

Federal regulations permit BU and BMC to delegate its IRB review responsibilities to the IRB of another institution that holds a Federal Wide Assurance (FWA). BU/BMC makes these decisions on a case-by-case basis. As a condition of delegation of review, the BU/BMC IRB and the external IRB assuming review responsibility (known as the IRB of record) must enter into a signed Authorization Agreement (IAA) that defines the scope of review responsibilities. Both institutions retain a copy of the signed IAA.

BU/BMC may agree to enter into individual Authorization Agreements with assured institutions for review of individual studies. When such an agreement is in place those IRBs which BU/BMC will rely on for IRB review are listed on the OHRP website under BU/BMC's FWA.

In certain instances, BU/BMC investigators may wish to include co-investigators on their studies who are not engaged in research as employees or agents of a FWA "assured" institution or whose duties on the BU/BMC study are outside of their employment at an FWA institution. Under such circumstances BU/BMC may agree to extend its FWA to cover these non-assured investigators. In each case, an IIA (Individual Investigator Agreement) will be signed by both parties. The BU/BMC PI is responsible for the research conduct of the non-assured investigator. BU/BMC follows the OHRP guidance for this process <http://www.hhs.gov/ohrp/humansubjects/assurance/guidanceonalternativetofwa.htm>.

IRB Composition

The BU/BMC IRB panels are comprised of members from multiple professions, diverse cultural backgrounds, and both genders. Each panel includes members with knowledge of institutional commitments and requirements, the local community, local research, local context, and experience with vulnerable subjects. These panels are constituted with both scientific and non-scientific members in order to ensure diversity on each panel. At least one member on each panel has no affiliation with BU/BMC other than his/her membership on the IRB.

A list of IRB members identified by name, earned degrees, representative capacity, and affiliation with the institution is submitted to the Office of Human Research Protections in the BU/BMC IRB Registration. A list of each of the internal Panel members is posted on the BU/BMC IRB website (www.bumc.bu.edu/irb and www.bu.edu/irb). This list is updated as voting board members are added or removed from the panels.

The list of voting IRB members also contains the name of those who can serve as an alternate to vote for voting members who are not present at a meeting. Each board member is listed in one of four designated categories (Chair, MD-scientist, non-MD scientist, non-scientist). Any member from any panel or from the alternate list can serve as an alternate for any other voting member as long as he/she is listed in the same category. Each member alternate is routinely provided an agenda and copies of each protocol to be discussed at the IRB meeting electronically at least 5 days prior to the IRB meeting. Alternates who indicate their intention to attend a meeting are also provided these materials.

BU/BMC has an IRB Internship program where trainees spend two months attending IRB meetings as part of their learning experience. Trainees/ IRB interns serve as IRB reviewers, under the mentorship of experienced IRB members. Trainees are not members of the IRB and do not vote on approval of protocols.

IRB Board members

Selection and Appointment

IRB Chairs, with the Director of the IRB, determine the types of expertise required for review of research conducted by their Panels. Department Chairs, IRB administrative staff, board members and others may nominate potential IRB members to the Director of the IRB. The IRB Director is responsible for the

appointment of new board members. The Director informs the Institutional Official of changes in board membership. New members are named on the roster and reported to OHRP along with their qualifications and whether or not they are affiliated with the institution.

Orientation of new board members is primarily the responsibility of the IRB Educator as designated by the IRB Director. Under certain circumstances, in place of the IRB Educator, new IRB Board members may be oriented by a Board Chair or Vice Chair, the IRB Director, or a Senior IRB Analyst.

Length of Term/Service

The term for IRB member service is two years, renewable for subsequent one year terms. Appointments to the IRB are made annually for a one-year term.

Duties

BU/BMC IRB Board members are responsible for ensuring that the rights and welfare of research subjects are protected by reviewing and approving human research in a manner consistent with federal regulations, state and local laws, and institutional guidelines and policies. Board members attend IRB meetings and may be assigned as primary or secondary reviewers, or specialty reviewers of protocols. When assigned as a designated reviewer (primary, secondary or specialty) Board members submit their reviews of the protocols to the IRB staff.

Attendance Requirements; Alternate Members

Members attend their respective meetings, where attendance is noted in the IRB minutes. Voting board members may serve as alternates for other voting board members in the same category (Chair, MD/DMD-scientist, non-MD scientist, non-scientist). A voting member may only substitute for another member of any panel if such panel member is not available to vote (e.g.; absent, recused for conflict of interest). If more than one alternate member is present at a meeting where members are not present, only one alternate may vote for each absent member. The IRB Analysts assigned to each meeting are responsible for tracking alternates and ensuring that there is quorum present during the entire meeting.

Removal/replacement

IRB members may be removed or replaced by the Board Chair in collaboration with the IRB Director.

Leadership

Chair(s)

Selection and Appointment

The Institutional Official appoints the Chair(s) to the IRB. The Chairs' names and credentials are submitted to the Office of Human Research Protections by the IRB Director in the IRB Registration.

Length of Term

There is no set term limit for how long the Chair may serve as IRB Chair. Appointments are made annually for a one-year term.

Duties

The Chairs direct their Panel's proceedings in accordance with institutional and federal requirements, as well as parliamentary procedure. They work closely with the IRB Director, the Board Members, the IRB

Analysts, the IRB Educator, the Manager of Research Quality Assurance, other IRB Office Staff, institutional officials, and investigators to ensure that the rights and welfare of research subjects are protected.

The Board Chairs are the principal signatory officials for IRB correspondence. They may, however, delegate this responsibility to the Vice-Chairs, IRB Director, and IRB Analysts and IRB Board Members as allowed by the regulations and IRB policies. The IRB Chairs review and approve the minutes of each IRB meeting they conduct. The Chairs also may review expedited new protocols, amendments, and progress reports as well as reports of unanticipated problems, protocol deviations and exceptions. The Chairs conduct expedited review as allowed by the regulatory guidance (see Appendix B) and refer all other actions for review by the convened board. The Chairs may delegate the responsibility for reviewing some or all expedited protocols (including new protocols, amendments, progress reports, unanticipated problem reports, deviations and amendments to experienced voting board members (identified as Expeditors).

Removal/Replacement

Chairs may be removed or replaced by the Institutional Official.

Vice-Chairs

Selection and appointment

The Institutional Official may select and appoint one or more vice-chairs for the IRB panels. The Vice-Chairs' names and credentials are submitted to the Office of Human Research Protections in the IRB Registration.

Length of Term

There is no set term duration for the Vice-Chair's appointment, although appointments are made annually for a one-year term.

Duties

The Vice-Chair shares the same functions and duties as the Chair, as delegated by the Chair.

Removal/replacement

Vice-Chairs can be removed or replaced by the Institutional Official.

IRB Director

Selection and appointment

The IRB Director is selected and appointed by the Institutional Official. . The IRB Director is designated as the Human Protections Administrator on the Institution's Federalwide Assurance. The IRB Director reports to the Director of the Office of Clinical Research for administrative issues, and to the IRB Chairs and the Institutional Official for human subjects issues.

Length of Term

There is no set term duration for the Director.

Duties

The IRB Director serves as a regulatory consultant to the IRB Chairs, Vice-Chairs, and Panels. In addition the IRB Director has regulatory oversight responsibilities for the IRB and the IRB Office.

Removal / replacement

The IRB Director can be removed or replaced by the Institutional Official and/or the Director of the Office of Clinical Research.

IRB Administrative Staff

Selection and appointment

The IRB Director is responsible for the hiring of all IRB Administrative Staff (including Administrative Assistants, IT Support staff, IRB Coordinators, IRB Analysts and Educators). The Director may delegate this responsibility to a senior member of the IRB Administrative Staff as appropriate. Hiring of Administrative Staff is done through the Boston University Human Resources department.

Removal/replacement

IRB Administrative staff report to the IRB Director or (as designated) to a senior member of the IRB Administrative Staff. There is no set term limit for IRB Administrative Staff. The IRB Administrative Staff can be removed or replaced by the IRB Director in accordance with BU Human Resource policies.

Duties

The duties of the IRB Administrative Staff are specified in their job descriptions and described in Section IV of these policies.

IRB Executive Committee

Composition

The voting members of the IRB Executive Committee are the Chairs, the Vice-Chairs and the IRB Director. Advisory to this Committee, as non-voting members, are the Institutional Official and the legal consultant to the IRB. The Director of the IRB serves as the Chair of the IRB Executive Committee. Any one of the Board Chairs or Vice Chairs may serve as an Alternate Chair.

Responsibilities

The IRB Executive Committee provides leadership to the IRB Panels, by setting and approving policies and procedures. In addition, the Executive Committee provides a forum for discussions of regulatory interpretation, and to assure consistency among panels.

The Executive Committee plays a central role in reconciling non-willful discrepancies in the application of regulations or policies.

The IRB Executive Committee is responsible for ensuring the quality of the IRB activities at BU/BMC. The Executive Committee has delegated the direct responsibility for this oversight to the Manager of Quality Assurance (also referred to as the IRB Auditor) and the Director of the Clinical Research Resources Office. The Manager of Research Quality Assurance reports to the Director of the Clinical Research Resources Office for administrative issues and to the Board Chairs for Human Subjects Issues.

The Institutional Official

The Institutional Official (IO) must be legally authorized to represent the Institution providing the FWA. The Institutional Official (IO) is the Associate Provost of the Institution. The IO represents the institution as the signatory official on the FWA (Federal Wide Assurance). The IO may not be the Chair or a voting member of any of the institution's IRBs designated under the FWA. The IO signs all IRB Authorization Agreements and Individual Investigator Agreements but may delegate this responsibility to the IRB Director or one of the Board Chairs. Research matters related to investigator conduct or research non-compliance are referred to the IO by the IRB.

Training of IRB Chairs, Vice-Chairs, and members

Orientation

IRB Chairs, Vice Chairs and members are provided with orientation materials as well as ongoing educational training materials. Orientation materials include, the Belmont Report, Department of Health and Human Services Protection of Human Services regulations 45 CFR 46, Food and Drug Administration regulations 21 CFR 50 and 56, Office for Human Research Protections (OHRP) Expedited Review Procedure, BU/BMC IRB Policies and Procedures, instructions on the use of the INSPIR program, and additional resource materials. In some cases written materials may be substituted with on-line links to these documents. In addition, new members are individually oriented by the IRB Educator (or a designated experienced board member or IRB Staff member). New board members attend at least one IRB meeting as an observer before voting at a meeting. New board members attend at least two meetings as a voting board member before being assigned as a primary or secondary reviewer. The IRB Educator or an experience board member serves as a mentor for the new board member at least for his/her first formal review as a primary or secondary reviewer.

Experienced, voting Board Members may be designated by one or more Chairs to review protocols via the Expedited review process. These board members are referred to as Expeditors. Experienced IRB Analysts may serve as Expeditors. All Expeditors receive additional training related to the expedited review process by the IRB Director or designee.

Continuing Education for Board Members

Brief board education sessions are regularly provided to board members by the IRB Director (or designee) at the start of the IRB meetings. These sessions cover both general research related topics, regulatory issues, protocol specific questions, or the most recent topic of the CR Times feature article. IRB members are also strongly encouraged to read the CR Times each month. (The Clinical Research Times is a monthly on-line newsletter published by the BU/BMC Office of Clinical Research. Copies may be found at www.bu.edu/crtimes) Board members are also invited to attend the Clinical Research Seminar Series, a monthly seminar sponsored by the Office of Clinical Research,

Reference materials (IRB library)

Reference materials may be found in the Boston University Medical Center library, the IRB office, or specific URL links located on the BU/BMC IRB websites (www.bumc.bu.edu/irb and www.bu.edu/irb). These links include the OHRP website, FDA website, and other related IRB and human research protection websites. The BU/BMC IRB websites may be accessed by BU/BMC and non-BU/BMC investigators, IRB staff and board members via the internet.

Compensation of IRB Members

Most members are not routinely compensated for their work on the IRB. However, certain members, such as Chairs, Vice-Chairs, and statisticians, are compensated for their time, through funding given directly to them or through their department. Some compensation may be provided to board members at the discretion of the Director under special circumstances such as performing review of expedited and exempt protocols. Board members may be reimbursed for some expenses related to their IRB participation such as parking and internet access.

Liability Coverage for IRB Members

IRB member liability is covered by the Boston University and the Boston Medical Center insurance policies. Each member is provided with an indemnification letter from these two institutions.

Use of Consultants

IRB panels use non-member consultants for advice and information in specialized areas as needed. These consultants may be BU/BMC faculty, staff, or students, or may be unaffiliated with BU/BMC. The final determination on whether a consultant will be used for a protocol rests with the Board Chair or IRB Director. The IRB may at times ask the investigator(s) for recommendations regarding appropriate consultants. The consultants may present their assessments in writing or in person for board meetings. These consultants do not vote during IRB meetings and are bound by the same confidentiality and conflict of interest requirements as all other attendees at an IRB meeting.

IRB Member Conflict of Interest Policy

Reviews of IRB protocols are conducted with objectivity and in a manner designed to ensure the exercise of independent judgment of each member. Members may not participate in a vote by the IRB on actions concerning projects or activities in which they have an active role or a conflict of interest (financial or other). Knowing failure to abide by these requirements may be cause for removal of a member from the IRB.

IRB members do not vote on protocols on which they are an investigator (PI or co-investigator) or if they declare any type of conflict of interest with any person or entity connected to the protocol. Each IRB member is responsible for making any conflict of interest known to the IRB Chair and recusing him/herself from the portion of the meeting during which discussion and voting on the protocol in question occurs. This conflict is documented in the IRB meeting minutes. Depending on the nature of the conflict, the member who has identified the conflict may be allowed to participate in the IRB discussion to provide the IRB with information about the protocol prior to the final discussion and voting on the protocol. This is done at the discretion of the meeting Chair. The fact that a protocol is submitted by another investigator from an IRB member's Department or Section does not, in and of itself, constitute a conflict of interest.

At the start of each IRB meeting the meeting Chair reads a statement regarding conflict of interest reminding each member that he/she must recuse himself/ herself from the vote and leave the room if there is any actual or potential conflict of interest. Board members receive updated training about Board Member COI annually.

IRB Office Staff and Administration: Analysts, Coordinators, IT Applications Specialist and Secretarial support and resources

The BU/BMC IRB Office provides administrative support for the IRB panels, maintaining one administrative office on the Charles River Campus and one at BUMC. The IRB Director (who directs both offices), the IRB (INSPIR) Application Specialist/ IT Administrator, the IRB Analysts and Coordinator(s) and the IRB Office Administrative Support Staff serve as communication links between investigators and IRB panels.

Experienced IRB staff members may be appointed to the IRB as voting members by the IRB Director in consultation with the IRB Chairs. The IRB Director may recommend to the IRB Chairs experienced IRB Analysts who are qualified to serve as Expeditors. Experienced Board members (including members of the IRB staff) may be appointed as Expeditors by the Chairs.

The IRB Analysts' and coordinators' responsibilities include but are not limited to:

- Reviewing IRB protocols to determine whether they are complete or required administrative deferral
- Assigning protocols to appropriate reviewers (full board or expedited)

- Reviewing protocols and working with investigators to ensure that requirements are met
- reviewing consent forms and making suggestions for improving consent documents
- performing expedited reviews when designated to do so by the Board Chairs
- generating electronic modification memos to investigators on behalf of the Board Chairs or Expeditors
- generating approval letters on behalf of Board Chairs and Expeditors
- recording the meeting minutes, transcribing minutes, presenting the minutes to the Board for vote; sending the approved minutes to the IO
- Experienced IRB Analysts and IRB Coordinators, at the discretion of the IRB Director may be appointed to one or more IRB Panels as voting members or alternates. The Board Chairs may, at their discretion, designate experienced IRB Analysts as Expeditors who may process expedited actions (such as review of new expedited protocols, review of expedited progress reports, review of amendments which do not change risks to subjects, etc.) These persons are listed as voting members or alternates on the BU/BMC OHRP IRB Registration.

BU/BMC provides the IRB offices with appropriate office space, equipment and other support to perform their functions. Filing cabinets located in a locked file room in the IRB office contain paper documents related to active protocols. Closed paper protocols are stored in the locked file room in the IRB offices or in an off-site secure records management facility.

Electronic IRB Review on the Medical Campus

As of March 2004 the BU medical campus and Boston Medical Center implemented an electronic system called INSPIR (Integrated System for Subject Protection In Research) for the submission, review and documentation of protocols to the IRB. Since March 15, 2004 all new medical campus protocols have been submitted to the IRB using the INSPIR format. Studies that were approved prior to the March 15, 2004 and were still ongoing at that time were converted from the paper format to the electronic format.

All IRB documents submitted or created after implementation of INSPIR are stored within the INSPIR system. This system maintains the confidentiality of the records in accordance with BU/BMC OIT policies and is compliant with 21 CFR 11. The INSPIR system is maintained by an Application Specialist and the BU/BMC OIT department under the direct responsibility of the Director of the IRB.

To gain access to INSPIR investigators must be registered in the INSPIR system and the BU Active Directory. The BU/BMC OIT department processes the registration application, contacts the investigator with instructions as to how to activate the account, and provides an investigator with user name and password for INSPIR.

Each investigator in the INSPIR system receives an individual secure, unique user name and password. This user name and password serves as an electronic signature within the INSPIR system. BU/BMC OIT policy specifically prohibits the sharing of passwords or the use of another's password.

IV. IRB Office staff

Responsibilities

The primary responsibility of the BU/BMC IRB Office staff is to support the IRB Panels and Chairs as they fulfill their review and other regulatory responsibilities.

The general responsibilities of the Office of the IRB include, but are not limited to:

- Receipt and tracking of new IRB protocols.

- Preliminary screening of protocols and other IRB submissions to determine if they are complete and ready for IRB review
- Initial review of submissions to identify regulatory, legal or ethical issues
- Preliminary review of informed consent forms to determine if the required elements are present, and to assess clarity and simplicity of the language.
- Initial determination as to whether a protocol represents human subjects research, qualifies as Exempt or requires review by the Expedited Process or a full (convened) panel
- Preparation and distribution of agendas for IRB meetings
- Preparation of the minutes of each IRB meeting
- Submission of the minutes to the Institutional Official
- Prompt notification of the PI of the outcome of IRB meetings and any actions taken related to his/her protocol
- Receipt and review of all correspondence (including amendments, modifications, progress reports, exceptions, deviations, AEs, SAEs, etc.) related to existing protocols.
- Assignment of protocols to reviewer(s) and communication with the PI regarding the results of the review.
- Receipt and processing of Progress Reports. Notification of PIs regarding the outcome of Continuing Reviews.
- Maintenance of complete, organized, and easily assessable IRB records, with particular attention to the integrity and security of the IRB records.
- Communication Investigators regarding any research subject complaints received by the Office
- Provision of education and assistance to investigators regarding IRB related issues
- Facilitation of communication among IRB Chairs/Vice-Chairs, IRB Panel members and Investigators

Administrator

In the absence of a designated IRB Administrator the following responsibilities are delegated to the IRB Director, who may then assign them accordingly.

The IRB Administrator is responsible for the day to day operations of the Office of the IRB. The IRB Administrator allocates responsibilities within the office to IRB analysts, coordinators, the applications support specialist and administrative staff in order to ensure completion of tasks. The IRB Administrator directly reports to the IRB Director and is accountable to the IRB Chairs for the timeliness and accuracy of administrative tasks completed for the IRB.

The IRB analysts and coordinators process and review IRB submissions according to the procedures described in this document. Exceptions to these procedures must be approved by the Administrator or Director of the IRB.

The Administrator provides ongoing oversight and evaluation of the administrative processes in the Office including but not limited to

- Status of the study files (organization and completeness)
- Adequacy and completeness of the minutes and agendas
- Timeliness of continuing reviews
- Timeliness and accuracy of letters to investigators
- Timeliness and accuracy of processing protocols and other IRB submissions (i.e. amendments, AEs, etc.)

The Administrator makes changes to internal processes (SOPs) as required to ensure that the Office is compliant with regulations and BU/BMC policies and procedures.

IRB Analysts, Coordinators and Administrative Staff

The IRB Analysts and Coordinators process and review IRB submissions according to the procedures described in this document and internal processes (SOPs) developed by the Office of the IRB. Exceptions to these procedures must be approved by the Director of the IRB.

IRB Records

The Office of the IRB maintains IRB records in a confidential manner either in the Office of the IRB, in a secure off-site records management facility, or in password protected, secure, electronic systems (including INSPIR). Original study files are not removed from the Office of the IRB without the permission of the Administrator or Director of the Office. The records may be inspected and copied by the Food and Drug Administration (FDA), Office of Human Research Protection (OHRP), other federal or state government agencies, hospital accrediting agencies, or others, as appropriate. It may take up to 3 business days for the IRB to obtain records stored in the off site facility. The Director of the IRB is responsible for the IRB records but may designate the day to day responsibility for managing the IRB records to a member of the IRB Office staff.

The IRB retains study records including approved protocols, consent forms, recruitment materials, etc. for a minimum of 3 years after completion of the study.

The Office of the IRB contracts with a certified vendor to shred paper IRB documents and materials that are no longer needed.

The Office of the IRB maintains IRB records, including but not limited to the following:

- **IRB Membership Roster** The IRB Roster includes names of members, alternate members, ex officio (non-voting) members' names; earned degrees; specialty and relationship to Boston University or Boston Medical Center. The IRB membership roster is submitted with the IRB Registration to OHRP. A copy of that registration is kept on file at the Office of the IRB. The IRB posts a copy of its membership roster on the IRB websites www.bumc.bu.edu/irb and www.bu.edu/irb.
- **Written Procedures and Guidelines**
FDA (21 CFR 56) and DHHS (45 CFR 46) require that an IRB operate according to written Policies and Procedures to ensure protection of the rights and welfare of individuals involved as subjects in research. These Policies and Procedures are approved by the IRB's Executive Committee, reviewed periodically, and updated as needed. Any person wishing to suggest a new policy or revision to a current policy must submit the suggestion in writing to the IRB Director along with the rationale for the change/addition. The Director reviews the proposal and presents it to the Executive Committee for consideration. A copy of the most recently approved version of the IRB Policies and Procedures is posted on the IRB websites www.bumc.bu.edu/irb and www.bu.edu/irb.
- **IRB Records, including Protocols Reviewed, Approved Informed Consent Forms, and Correspondence**
While the study is still active, any existing paper IRB records related to the protocol are maintained in the IRB office. After study closure, paper records are retained in the IRB office or at an off-site secure storage facility for a minimum of three years, or longer if required for a particular study. Electronic records are stored indefinitely in the electronic INSPIR system. The IRB does not produce hard copies of all of these documents. Board members are instructed to observe confidentiality rules when using these documents to perform their IRB reviews. They are instructed not to share these documents or to use these materials for any use other than to conduct their IRB review.

At the discretion of the IRB Director and/or Board Chairs, access to IRB electronic files is granted to other BU/BMC offices including the Office of Research Compliance, Office of

Sponsored Programs, BMC Office of Grants Administration, the Clinical Research Resources Office, Conflict of Interest Advisory Committee, Institutional Biosafety Committee, Human Gene Therapy Committee, GAC (GCRU Advisory Committee, etc.). All those who are granted access are required to maintain the confidentiality of the documents and only use them for the purpose granted.

- **Minutes of all IRB meetings** (hard copies) are signed by the Board Chair and stored in the IRB Office. An electronic copy of the minutes is retained in a password protected electronic “department” folder in the BU/BMC electronic database. A copy of each set of minutes is sent to the IO after they have been approved by the Board. The original signed version of the IRB minutes are not removed from the IRB office without the permission of the IRB Director or Administrator. The IRB minutes are confidential documents. They are released to board members (including the ex-officio board members) for their review and are subject to the same confidentiality rules as other IRB materials. The minutes of the board meetings are not released to investigators or sponsors or other departments unless approved by the IRB Director. Board members are reminded not to share these documents with others who are not board members or members of the IRB staff. Board meeting minutes are shared with regulatory agencies (i.e. OHRP, FDA,) as required by the regulations.
- **Other documents related to IRB meetings** (agenda, reviews by primary/secondary reviewers, educational materials, etc.) are either stored in paper form in the IRB office or are available via the INSPIR system. The IRB does not produce hard copies of all electronic documents in the INSPIR system. The IRB does not retain audiotapes of IRB proceedings that may have been used temporarily by the staff to help record the proceedings of the IRB meetings. Board members are reminded during IRB meetings that IRB documents are confidential and are not to be used outside the IRB context except with the permission of the IRB Director.
- **Executive Committee meetings** - Documentation of the proceedings of the IRB Executive Committee meetings and related communications are retained by the Director of the IRB or the Chair of the committee.
- **Communications to and from the IRB**
After March 15, 2004 IRB communications at the medical campus are documented in the electronic format in the INSPIR study “file”. In some cases paper documents were added to the paper file until the study was fully converted to the electronic format.

On the Charles River Campus formal communications with investigators to and from the IRB are filed in the IRB’s study file. Electronic communications (email) are printed and retained as hard copies. Records of these communications are maintained as part of the complete study file.

- **Reports of Unanticipated Problems (UPs) and Adverse Events and Data Safety Monitors’ Reports-** Investigators are directed to report to the IRB unanticipated problems and adverse events according to the SOPs described in <http://www.bumc.bu.edu/irb/reportingadverseevents/> .
- **Record of Continuing Review** Requirements for Continuing Review are provided to the Principal Investigator with the IRB Approval Letter. Deliberations and approvals of Continuing Review Progress Reports are documented in the minutes and filed in the electronic or paper study file. The IRB notifies investigators by emails of the need to submit Progress Reports at least 42 days prior to the study expiration date. These are considered courtesy reminders. It is the investigator’s responsibility to ensure the timely submission of Progress Reports for continuing review of protocols even if these courtesy reminders are not received. Documentation of these reminders is maintained in the INSPIR system or the study file. .

- **Emergency Use Reports** Instances of emergency use of a drug, device or biologic agent are documented in the INSPIR system or in a paper file. The practitioner who uses the drug or device must notify the IRB within 5 working days of use of the emergency article. Reviews of emergency use are reviewed by the IRB and documented in IRB minutes.

- **Statements of Significant New Findings Provided to Subjects** The requirement to provide information to subjects regarding significant new findings is included in the consent form when deemed appropriate by the IRB. The method and urgency of conveyance of new findings varies depending on the nature of new information to be provided. Significant new findings are reviewed by the IRB before changes are made to the protocol unless immediate action is needed to prevent immediate harm to subjects. For example, if a study medication is harmful, then all patients will be notified immediately. In less urgent cases, written notification may be appropriate. In addition, a telephone call may be necessary. A revised consent form with or without the re-consenting of all affected subjects may be necessary. Verification that these notifications were done may be required by the IRB. The PI must maintain documentation of this notification in his/her files and this must be available for audit.

- **Other materials related to the operations of the Office of the IRB** Records related to the orientation and training of IRB office staff, IRB office staff meeting proceedings and agendas, and internal processes/ SOPs are maintained by the IRB Director or designee.

- **Administrative forms used by the Office of the IRB** The IRB Director is responsible for the management of paper and electronic forms used by the IRB. New forms are approved by the Director prior to use. Any person wishing to suggest a new form or revision of a current form must submit the suggestion in writing to the Director along with a description of the rationale for the change. These requests are reviewed by the IRB Director, the Executive Committee, the IRB IT Application Specialist, the IRB Board members and IRB staff as appropriate.

V. IRB Meetings

Location

IRB meetings are held in suitable conference rooms on the Charles River and Medical Campuses of Boston University

Scheduling of Meetings

The panel on the Charles River Campus meets once per month. Panels Blue and Green (medical campus) meet as determined by a schedule set at the beginning of the academic year by the IRB Director (typically twice per month each). A schedule of the dates and locations of meetings is made available on the IRB website. Panel Purple meetings are scheduled when a determination is made by the Panel Purple staff, the Board Chair and the Director that there are sufficient protocols to warrant a meeting (typically once per month). The agendas for meetings are set and sent to the board members at least 5 days prior to the meeting. Scheduled meetings may be canceled or rescheduled for holidays, a lack of

quorum, or if the institutions are closed due to weather. Meetings are cancelled or rescheduled by the action of the Panel Chair(s) in conjunction with the Director.

Confidentiality of Materials and Discussion

At the start of each IRB meeting the IRB Chair reads a confidentiality statement such as the following: "All proprietary information or trade secrets that you have access to as a result of this meeting and all discussions that take place at this meeting are to remain confidential. All printed materials, excluding educational materials should be given to the IRB staff or placed in the shredder bin." A copy of the confidentiality statement is placed on each agenda.

Visitors

Visitors are allowed to attend IRB meetings with the permission of the Panel Chair(s) or IRB Director. Visitors may request permission to attend IRB meetings by contacting the Director or one of the IRB Analysts. Visitors must agree to sign a statement of confidentiality prior to attending any IRB meeting. Visitors are not allowed to remove any written materials that are distributed during the meeting from the meeting with the exception of educational materials. If during an IRB meeting the Chair moves the meeting to Executive Session then visitors are asked to leave the room until the Executive Session has ended.

If a protocol on the meeting agenda involves the visitor (as an investigator, member of the study staff, etc.) then the visitor must make that his/her interest in that protocol known to the Board Chair or IRB staff. The visitor may be allowed to stay in the meeting during the presentation of the study (at the discretion of the Board Chair), but the visitor must leave the room during the final discussion and vote on that protocol.

For situations where visitors may not be members of the study staff, the IRB Chair retains the right to ask any visitors or non-voting IRB members to leave the room during the discussion and or vote of any protocols or agenda items.

Quorum / Voting Procedures:

After discussion of the protocol, the IRB members vote on their decision about the protocol, which can include approval, conditional approval (conditions that require simple concurrence on the required review criteria ([45.CFR 46.111](#), [25 CFR 56.111](#)), deferral, and disapproval. Votes (for, against, abstain), those recused, and the attendance are recorded in the minutes. The IRB observes the following rules in its voting:

- (1) A Quorum Required to Transact Business
One half of the total number of "active" voting board members plus one must be present to achieve a quorum.
- (2) Diversity Requirements of Quorum
At least one member whose concerns are non-scientific must be present. At least one physician member must be present when reviewing studies with FDA regulated drugs, biologics, devices.
- (3) Percent needed to approve or disapprove study
A motion is made to approve, conditionally approve, defer or disapprove a study. In order for the motion to pass it must be agreed upon by a majority (>50%) of the voting members present (including those who have abstained or recused themselves).
- (4) Full voting rights of all members
 - Each member has one vote. If the member is unable to vote (absent or recused), then one appropriately designated alternate member may vote in place of the member.
 - Ex-officio members are non-voting members.
 - A board member may attend the meeting via teleconference and may vote during the meeting at the discretion of the Board Chair. This member must have been

provided access to the meeting materials including the agenda and reviews by the reviewers prior to the meeting.

(5) Proxy votes (written or telephone)

No proxy votes (written or telephone) are allowed.

(6) Prohibition against conflict-of-interest voting

Members who have a conflict of interest may be present to answer question about the protocol but then are required to leave the room and recuse themselves from deliberations and voting. The presence of a conflict and the recusal are recorded in the minutes.

Minutes and Agendas

Meeting agendas and minutes are prepared for each convened IRB meeting. Each IRB panel reviews and approves the minutes of its previous meetings during subsequent convened IRB meetings.

The BU/BMC IRB minutes document separate deliberations, actions, controverted issues, and votes for each protocol reviewed by the convened panel. Additionally, educational materials distributed and audits discussed are documented in the minutes. The IRB notifies board members of expedited actions taken on behalf of the board by providing board members access to these documents via the INSPIR system or by an electronic document. Board members are notified in each meeting agenda about how to access these studies.

Minutes contain, at a minimum

1. The date, time and location of the meeting
2. Documentation of voting and non-voting members present, absent, and recused and any alternate members replacing absent or recused members, and any visitors
3. When a member joins or leaves the meeting, and any loss of quorum
4. Attendance of staff, ex-officio members and guests
5. Educational materials distributed/discussed
6. Actions taken by the IRB at the meeting on any of the following
 - initial reviews
 - continuing reviews
 - amendments (including safety or investigational brochure updates)
 - unanticipated problems or adverse events
 - resubmitted protocols
 - protocol deviations
 - non-compliance issues, study terminations or suspensions
 - audits of research protocols
7. All votes on actions, including number of members voting for, against, those recusing themselves from voting (and discussion) and those abstaining from voting on actions
8. Administrative issues
9. Summary of discussion of issues pertaining to protocol reviews, particularly controverted issues
10. The basis for requiring changes in or disapproval of research, and any subsequent resolution of those requirements or disapproval
11. Any determinations regarding waiver of the requirement for informed consent, for waiver of informed consent documentation, or for waiver of particular elements of informed consent.

12. Any determinations regarding regulatory categories and justifications for research involving pregnant women, fetuses, prisoners, or children
13. Findings made by the board related to 21 CFR 312.2 and 812.2.
14. The results and issues pertaining to audits of research conducted by the IRB
15. The Waiver of HIPAA Authorization

Notification of IRB Actions to the Institutional Official

The BU/BMC IRB office staff sends the IO electronic copies of the minutes of each IRB meeting after the minutes have been approved by the board.

Communication with Investigators Conveying the Outcome of IRB Meetings

IRB actions that occur during IRB meetings are promptly conveyed to the Principal Investigator by the IRB office staff.. Communications include conditional approval and its conditions, or deferral or disapproval including the reasons for non-approval. Letters and minutes may suggest changes to the protocol and/or consent form required before the protocol will be reconsidered by the Panel. The Board Chair, a board member or the IRB Educator may volunteer or may be assigned to work with the Principal Investigator to address the IRB's concerns about the protocol.

The requests for protocol modifications that are provided to investigators convey specific requirements related to the board's decision, such as requirements for consent, waiver of consent, or waiver of certain elements of consent, conduct of the research as it related to special populations, the time requirements for resubmission for consideration or renewal, any other protocol specific requirements determined by the IRB.

VI. Principal Investigators, Co-investigators and Other Research Personnel

Qualifications to Perform Human Research

Per institutional definition, **investigators are** those who have contact with research subjects or their identifiable data in the performance of any research related activities (i.e. enrollment, consenting, collection of study data, interventions, long-term follow-up or data analysis). The IRB staff uses the OHRP engagement guidance <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html> to help determine whether a researcher is considered "an investigator engaged in the research".

The PI is required to list on the IRB protocol all investigators who will be engaged in the research under BU/BMC's FWA. As part of the review process the IRB staff verifies that all investigators listed on the protocol have provided documentation of human subjects research training.

All non-BU/BMC investigators listed on the protocol must be supervised by the PI or one of the investigators (as appropriate) who is a member of the BU/BMC faculty or staff. Non-BU/BMC investigators must conduct all research related activities under their own FWA "assured" institution's IRB approval, or must conduct research under an approved Authorization Agreement (IAA or IIA) between their institution and BU/BMC.

SOPs for research involving other institutions:

<http://www.bumc.bu.edu/irb/researchinvolvingotherinstitutions/>

Students conducting research at BU/BMC research are, in general, subject to the same requirements for IRB review of research as other investigators. Some student related activities are not considered to be engagement in research. SOP for student research can be found at :

<http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/students%20in%20research.rev.2.pdf>

Information regarding student research conducted on the Charles River Campus can be found at www.bu.edu/irb under Student Research.

Requirements for Principal Investigators

Principal Investigators (PIs) must possess the appropriate background, training, and professional qualifications to conduct the research required for each study. Each investigator listed on the protocol must possess the appropriate license(s) and institutional privileges to perform the research activities assigned to them in the study. It is the responsibility of the PI of the study to ensure that all research related activities in the study are assigned to those members of the study staff who have appropriate licenses, qualifications and privileges so that the rights and the welfare of subjects are protected.

To serve as the PI on a BU/BMC research protocol an investigator must be a member of the faculty or staff of BU, BMC or one of the institutions affiliated with Boston University Medical Center. Investigators with Conflicts of Interest cannot serve as the study PI (except when exception is granted by the IRB.) Non-BU/BMC employees or those otherwise not affiliated with BU/BMC may not serve as the PI for protocols submitted for approval to the BU/BMC IRB. Exceptions to this policy may only be made by the IRB Director in collaboration with the Institutional Official.

On the Charles River Campus, students in masters or doctoral degree programs may serve as PI; their research mentor must serve as co-investigator. Undergraduate students may not serve as PI, but they can serve as co-investigators.

On the medical campus, professionals in training (students, interns, residents, pharmacy interns) are not permitted to be Principal Investigators. Fellows may be principal investigators only if they have attending privileges at BU/BMC or are faculty at BU.

Required Human Subjects Researcher Training and Certification

All investigators (as defined above) must be trained and certified in the protection of human subjects in order to conduct clinical research at BU/BMC. Initial training and certification can be obtained through human subjects protection training seminars offered regularly at BU/BMC, from CITI, through NIH's online training, or through other training opportunities (including in some instances training provided by another institution) as approved by the IRB Director or designee.

Investigators whose primary appointment is at BU/BMC (including all investigators serving as the PI on any study) are required to meet BU/BMC's human subjects research recertification requirements. Recertification can only be accomplished by correctly completing a series of questions related to educational articles distributed in the Clinical Research Times [www.bu.edu/crtimes], an electronic clinical research newsletter. Investigators who have not met the institution's recertification requirements are not allowed to submit new protocols to the IRB and are not allowed to be named as PI or co-investigators on any new protocols or added to existing protocols until the recertification requirements have been met. The details regarding the institution's certification and recertification are posted on the Office of Clinical Research website www.bumc.bu.edu/ocr and in the CR Times www.bu.edu/crtimes. Investigators can not meet BU/BMC's recertification requirements by attending training at other institutions or repeating the initial certification activities.

The BU/BMC IRB may require that a physician with admitting privileges and appropriate expertise be substantively involved with the research project, particularly if the research study or procedures are greater than minimal risk. (For definition of minimal risk see Appendix C of these policies). The determination as to the qualifications necessary for the study staff on each study are left up the IRB panel or expediter that reviews the study.

The BU/BMC IRB may determine that a proposed PI may not serve as the PI on a proposed study. This determination may be made because of an investigator's conflict of interest, previous serious or continuing non-compliance by an investigator, lack of licensure, medical staff membership, or sufficient qualifications to adequately oversee a specific research protocol, or other reasons deemed appropriate by the Board. In such cases the Board notifies the investigator in writing as to the reasons why he/she may not serve as the PI for the protocol.

The designation of the PI of record must be consistent across research documents, including the IRB application, General Clinical Research Center application, and informed consent form. The grant application for potential funding sources may list another principal investigator; however, the PI of record on BU/BMC research documents should be listed as a co-investigator on the grant application.

International research projects conducted through BU/BMC must have a PI at BU/BMC, who is responsible for communications with the BU/BMC IRB.

Communication between IRB and Investigators

The PI has the ultimate responsibility for the conduct of the research and this responsibility cannot be delegated. The PI is ultimately responsible for all communication with the IRB (via the Office of the IRB) regarding that research. While the PI may delegate these responsibilities to members of the study staff such as study coordinators and administrators it is still the PI's responsibility to verify the accuracy of all correspondence. All communications via INSPIR are password protected and investigators are informed that it is against institutional policy for them to allow others to use their INSPIR password. PIs may allow other members of the study team to develop and revise new IRB protocols, modification memo responses, amendments, and progress reports. However, these documents require the formal approval of the PI before they can be submitted to the IRB.

While all official IRB correspondence is directed to the PI, the PI may request that other members of the research staff also receive communication from the IRB. In the eyes of the IRB it is the PI who is ultimately accountable for the accuracy of the entire protocol and all its associated documents and attachments.

The IRB may request additional information from the Principal Investigator or the sponsor to enable appropriate review of research applications. Communications with the investigators are conducted electronically via modification memos. This documentation of communication between investigators and the IRB is maintained and this documentation may be viewed by the IRB as well as the investigators. It is the responsibility of investigators to maintain adequate research records including documentation of communications with the IRB.

The IRB is ultimately responsible for determining which materials and information are necessary to enable a thorough review of research to ensure that it conforms to applicable regulations and federal guidance. Protocols may not be assigned to a board meeting agenda if they are incomplete or do not contain the required signatures. Protocols are administratively deferred back to the PI so that outstanding issues may be addressed prior to assignment to a board meeting or expediter.

Training of Investigators

The institution conducts regular training and education in protection of research subjects for PIs and research staff. In addition, the Office of Clinical Research conducts a regular Clinical Research Seminar series, and maintains the records of attendance for both trainings. Ongoing education in human subjects research is available to investigators via the Clinical Research Times. Boston University offers a number of courses in human research which are available to BU faculty and staff.

There are 5 or more IRB Analysts on staff to assist investigators with questions and concerns regarding their IRB protocols. The BU/BMC has a Senior IRB Analyst who functions in the role of IRB Educator.

This person is available to investigators to answer general research related questions, assist with regulatory interpretation or to answer specific questions regarding BU/BMC policies and provide orientation to new investigators about IRB submissions.

The BU/BMC Clinical Research Resources Office <http://ctsi.bu.edu/index.php/research-resources/clinical-research-resources-office-crrro/> provides support to investigators conducting clinical trials

Investigator Conflict of Interest

As part of their IRB application, all BU/BMC Investigators must complete a Protocol Specific COI Disclosure (PSD) for each project. These PSDs are submitted to the appropriate office as described here <http://www.bu.edu/research/compliance/financial-conflict/forms/>.

For protocols where there is determined to be a COI, the conflict is reviewed by the institutional COI Advisory Committee. This committee makes determinations regarding how to minimize, manage or eliminate the COI. Notification regarding the COI Committee's determinations is sent to the IRB Director who informs the IRB Panel or Board Chair/Expediter. The IRB may then accept the recommendations of the COI Committee or make additional recommendations regarding the investigator(s) COI.

PI Responsibilities when Conducting Research at BU/BMC

PI is required to follow the regulations and conduct research in an ethically and morally correct manner.

General Responsibilities

- Follow the regulations and conduct research in an ethically and morally correct manner
- Ensure prompt reporting to the IRB, appropriate institutional officials and DHHS and/or FDA of all required documents and materials
- Maintain the privacy of data and protect the confidentiality of subjects regarding their identity and their private information
- Submit all required documentation including complete applications, progress reports, and amendments, protocol deviations and exceptions promptly to the IRB
- Report all Unanticipated Problems, AEs / SAEs, and Safety Monitors' Reports to the IRB in accordance with the plan described in the IRB approved protocol. BU/BMC IRB policy and SOPs for reporting of Unanticipated Problems, Adverse Events, and Safety Monitors' Reports to the IRB can be found at <http://www.bumc.bu.edu/irb/reportingadverseevents/>.
- Report all adverse events to the sponsor, the FDA, and the safety monitor (i.e. Data Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), AE Monitoring Committee, etc.) according to the sponsor's requirements, the FDA regulations for FDA studies, and the protocol DSMP (Data Safety Monitoring Plan).
- Maintain compliance with all HIPAA research requirements

Continuing Review

Continuing Review of research is conducted in accordance with 45 CFR 46.109 and 21 CFR 56.109.

The IRB must continually review ongoing research projects. Requirements for continuing review are provided to the PI in the IRB approval letter. The PI is responsible for submitting a Progress Report and updated Informed Consent Form(s) (when applicable) to the IRB for review and approval prior to expiration of the study. Many research protocols only require annual review but some research projects (e.g. those with higher risks) may require more frequent review. The required frequency of review is determined by the IRB and is clearly spelled out in the IRB approval letter.

Continuing review is substantive and meaningful as the IRB applies the same criteria for approval of continuing review applications (progress reports) as it does for initial applications (45 CFR 46.111 and 21 CFR 56.111). The Progress Report contains the following information: the complete, approved IRB protocol, protocol status (pending/no accrual, active, closed to accrual, completed, open for data analysis, open for long-term follow-up only), accrual information, accrual categories, reports of unanticipated

problems and adverse events, subject complaints, amendment information, protocol exceptions, protocol deviations, protocol findings and any presentations or publications of study findings. In addition, any additional information concerning the state of knowledge about the study question (particularly other information that might change the assessment of clinical equipoise or the risk: benefit assessment) is presented as part of the progress report.

Based on the information provided in the Progress Report and as allowed by the regulatory guidance, the staff in the IRB office determines whether the progress report can be reviewed by a board member who is a designated expediter or whether it must be reviewed by a convened IRB panel. Progress Reports submitted for continuing review may be expedited when the research was

- Approved by expedited review (as an expedited study) on initial approval and no changes in risks have occurred
- Approved by convened IRB but the research is now closed to enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects
- Approved by convened IRB but no subjects have been enrolled (at this site) and no additional risks have been identified
- Approved by convened IRB but now the remaining research activities are limited to data analysis
- Not conducted under an investigational new drug application or investigational device exemption, and the categories for expedited review for new protocols do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The office of the IRB notifies the PI that the research protocol is due to expire at least 42 days prior to the expiration date. It is the responsibility of the PI to ensure that the research protocol does not expire. The PI is required to submit the Progress Report at least six weeks prior to study expiration to allow the IRB time to process the submission. Failure of the PI to receive the renewal notice does not excuse the PI from his/her responsibility for submitting Progress Reports on time.

The continuation of research after expiration of IRB approval is a violation of the federal regulations. If the IRB has not received and approved continuation of a research study by the study's current expiration date, all study related activities must cease (including recruitment, enrollment, study interventions, long-term follow-up and data analysis) unless the IRB has made a determination that it is in the best interest of the subject(s) to continue. When a study expires, an email notification of the study expiration is sent to the PI

If there is a lapse in approval due to late Continuing Review

The IRB and investigators must plan ahead to meet required renewal dates. If a PI has failed to provide the IRB with a complete Progress Report or the IRB has not reviewed and approved a research study by the approval expiration date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of individual subjects to continue participating in the research interventions or interactions. If it is in the best interest of individual subjects to continue on the research protocol because there would be increased risks to the subjects if the protocol was stopped the PI must submit to the IRB a Protocol Exception. The exception must explain why it would be in the best interest for each individual subject or group of subjects to continue on the study during the lapse in approval. This Protocol Exception is reviewed by an IRB Chair or IRB Director and a formal determination is made as to whether some or all subjects already enrolled can continue. Enrollment of new subjects cannot occur. This is not and should not be seen as the IRB granting of an extension of approval for a study.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, approval of the study automatically expires. Such expiration (lapse in IRB approval) is not reported to OHRP as a suspension. The expiration of approval is reported by the IRB to the appropriate grants office.

Once approval for a protocol has lapsed, the PI must receive full IRB approval in order to re-institute the study. The PI is required to submit a Progress Report and a Protocol Deviation report. In the protocol deviation report the PI must describe the circumstances that led to the study lapsing and provide a corrective action plan (CAP) to ensure that this deviation will not occur again. Research activities cannot be re-instituted until the Protocol Deviation Report has been received and the Progress Report has been reviewed and fully approved. Failure by an investigator to submit timely Progress Reports may be determined by the IRB to constitute continuing non-compliance which may have to be reported to OHRP. (See Section XI of these Policies and Procedures under Serious or Continuing Non-compliance).

Reporting of an Unanticipated Problem (UP), Adverse Event (AE) and Serious Adverse Event (SAE)

Definitions

Unanticipated Problem- is defined at this institution as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents (such as the IRB-approved research protocol and informed consent document); and (b) the characteristics of the subject population being studied; AND
- is related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized OR are by definition **SERIOUS**. (Note: all incidents, experiences or outcomes that are unexpected, AND related or possibly related AND are **SERIOUS** are automatically unanticipated problems.)

Adverse Event (AE) is defined at this institution as, “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.”

Serious Adverse Event (SAE) is defined at this institution as, any adverse event that

- (1) results in death;
- (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- (3) results in inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant disability/incapacity;
- (5) results in a congenital anomaly/birth defect; or
- (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Unanticipated problems, SAEs and AEs are reported to the IRB according to the process described in <http://www.bumc.bu.edu/irb/reportingadverseevents/>.

Serious adverse events must be reported to the study sponsor and/or the appropriate federal agency as required by the regulations and the data safety monitoring plan in the IRB approved protocol.

- If the study involves an FDA regulated test article (IND or IDE held by the sponsor) investigators must notify the study sponsor. Investigators should check study protocol and procedure manual for details on what needs to be reported, how soon, and to whom.
- If the study involves an FDA regulated test article (IND or IDE held by the investigator), the investigator must notify the FDA directly. He/she may also need to notify the entity that holds the original IND for the investigational product being tested.
- For NIH-funded research, investigators are instructed to consult their Project Officers (different Institutes have different reporting requirements).

Unanticipated Problems, Adverse Events, and Safety Monitors reports are submitted to the IRB by investigators. The IRB website provides a description of the Institutional Policy for submission of AEs, SAEs, and UPs (unanticipated problems). Investigators are required to follow the procedures described in the IRB approved protocol.

- A. Each unanticipated problem (UP) involving risk to subjects or others (including those that are not AEs) that meets all 3 criteria of an UP, is reported to the IRB within 2 business days of the investigators learning of the incident.
- B. Each UP that is determined by the IRB to be a UP is reported to OHRP by the Director of the IRB within 10 working days of the IRB review. Copies of the OHRP report are sent to the Institutional Official, the Department Chair, the FDA (as appropriate), the study sponsor, the ORA/Grants Office, the IRB Manager of Quality Assurance the GCRC (as appropriate).The PI is copied on this letter.
 - Depending on the circumstances, a single report may be submitted or if indicated a preliminary report may be submitted initially and then a final report submitted when the final determinations have been made and any appropriate actions taken.
 - a. The notification (single report or final report) describes the IRB's action in response to the unanticipated problem including study suspension or termination, consent form or protocol modifications, any corrective action plan, or IRB intensive monitoring plan.
- C. A summary report of all AEs (including SAEs) that are NOT UPs are reviewed by the board (or expediter for expedited studies) as part of the continuing review process. This summary report is submitted at the time of the Progress Report.
- D. A formal report by the DSMB, DMC, or IRB approved safety monitor can be submitted to the IRB in lieu of a summary report of all AEs and SAEs.
- E. DSMB reports and other safety monitors reports are reviewed by the board as part of the continuing review unless more immediate action is indicated...
- F. If the report of an UP or a safety monitor's report indicates that there is a new or previously unrecognized risk to the study then the PI must submit an amendment to modify the protocol and consent (as appropriate) to reflect this change in risk.
- G. If an Unanticipated Problem is identified, the board may decide that no action is necessary, that the protocol and/or consent must be modified, that the study must be suspended or terminated or that other measures (i.e. additional safety monitoring) is needed.

After the study closes

If AEs and SAEs have occurred between the time of the most recent Progress Report and the time the protocol is closed, an AE summary report is submitted as part of the final report. A final report is submitted to the IRB using the Progress Report form. As with Progress Reports, the final DSMB report may be submitted in lieu of the AE summary report

Unanticipated problems must continue to be reported to the IRB for a minimum of 30 days (or longer if required by the IRB protocol) following completion of subject's participation or following closure of the study. If subjects must be notified of an unanticipated problem, a copy of the proposed notification letter must be included in the UPSER submission to the IRB. The IRB approves subject letters BEFORE they are sent to subjects unless they must be sent urgently to prevent immediate, serious harm to subjects. In

such cases the investigators must make every effort to contact the IRB office prior to sending the notification letters.

Amendments and Modifications to Protocols

Investigators are notified in their IRB approval letter that all changes that are not necessary to eliminate apparent immediate hazards must not be initiated without prior IRB review and approval. The investigators are required to conduct the study precisely according to the IRB approved protocol. No modifications, additions or other changes can be made to any of the research related activities (including minor changes to eligibility criteria, research interventions, recruitment methods, consenting procedures, etc.) without prior IRB approval unless necessary to eliminate immediate harm to subjects.

PIs request IRB approval for proposed changes in the research protocol by submitting an amendment request to the IRB office. The amendment includes a complete and detailed documentation as to what changes or modifications are being proposed, a justification for the changes as appropriate and an assessment of the impact of the changes on the risks to subjects. Along with providing an amendment description, the investigator must make the associated changes to the approved version of the protocol and consent form(s) (as appropriate).

Amendment requests that are submitted to the IRB are reviewed by the IRB Analysts. They are either then reviewed by a designated expediter (this may be the IRB Analyst if she / he is an Expediter) or assigned to a full board agenda to be reviewed by the IRB at a convened meeting. The determination as to whether expedited review or full board review is required is based on how the change affects the risk level of the study. Amendments to full board protocols are reviewed by the full board unless the amendment reflects only minor or administrative changes. When full board amendments are reviewed the findings are documented in IRB minutes. The IRB's decision regarding the amendment is provided to the PI.

The IRB may conduct an audit of any research protocol (by the Manager of Research Quality Assurance or other parties designated by an IRB Chair, Vice Chair or the IRB Director) if there is reason to suspect a changes have been made to the protocol prior to or without the approval of the IRB.

Protocol Deviations

Protocol deviations represent incidents, circumstances or processes that occur during the research protocol that are not part of or are inconsistent with the approved IRB protocol, with these set policies and procedures or with the Federal regulations.

Investigators are required to follow the IRB approved protocol. Once the PI or any member of the study team identifies an instance where the approved protocol has not been followed this must be promptly reported to the IRB on a Protocol Deviation Report.

Protocol deviations are reviewed a member of the IRB staff who consults with the Manager of Research Quality Assurance, with the IRB Director, the Board Chair, the Board, the IO and/ or the IRB Executive Committee depending on the seriousness of the deviation. PIs are required to provide the IRB with CAPs (corrective action plans) for all deviations which explain how the PI will prevent the deviation from recurring. The IRB may approve, request modifications to or disapprove CAPs.

Those protocol deviations that represent serious or continuing non-compliance with the federal/state regulations or institutional policy may be reported to the Institutional Official, OHRP, the FDA (if appropriate), the study sponsor, the appropriate grants office, the Board Chair and the PI's department Chair. The institution follows the OHRP guidance http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html in determining which protocol deviations constitute incidents reportable to OHRP.

Frequent or serious protocol deviations can cause the IRB to institute an audit of a research protocol and referral to the appropriate institutional research oversight committee.

A listing of all protocol deviations is available to the board at the end of each progress report. The board uses the information in the protocol deviations report and the Corrective Action Plan (CAP) in making its determination as to whether continuation of the research is appropriate.

Final Report

The PI is required to notify the IRB when his/her study is completed. The IRB considers the study to be complete when the primary data analysis is complete and the study question is answered. Timely final reports must be submitted when a study is closed or terminated by the PI or the sponsor prior to the anticipated end of the protocol. When a study is closed the investigator must describe the plan for destroying the study data and/or anonymizing the data.

A final report is submitted by the PI using the Progress Report form, indicating that the submission is a final report rather than a Progress Report for continuation of the study. Any presentations or publications of study findings that are available are attached to the protocol with the final report. It is not appropriate for investigators to allow their studies to lapse rather than submitting final reports.

Maintaining Research Records

It is the PI's responsibility to maintain all study records (including source documentation) according to federal requirements. All signed informed consent forms must be retained by the PI a minimum of three years after the end of the study. Under certain circumstances, as with INDs and IDEs, study records must be retained for longer than three years. It is the responsibility of the PI to be aware of these requirements.

The IRB retains the right to inspect any and all research records related to the study at any time during the active stage of the study, during follow-up and after the study has been closed. The IRB may conduct unannounced audits of research at any time. Failure by the PI to allow an IRB audit or to make all research materials available to the auditors could result in termination or suspension of the research project by the IRB and disciplinary action by Institutional Officials.

Transferring a protocol to another Investigator

If a PI leaves BU/BMC and/ or is no longer a member of the BU/BMC faculty or staff then all of his / her approved research studies must be either transferred to a qualified PI or closed.

When an investigator chooses to transfer his status as PI on an approved protocol to another investigator, the IRB is notified via an Amendment. The new investigator must be eligible to serve as a BU/BMC PI. The new PI must submit or have submitted the appropriate conflict of interest forms, must have documentation that she has completed the required human subjects protection certification and recertification and must have the necessary licenses and privileges required to serve as PI of the research protocol. Appropriate changes to consent forms, recruitment materials, etc. must be submitted with the amendment. The new PI is notified of the IRB approval of the change in PI.

VII. Research Protocols

Preparing a Protocol for Submission to the IRB

On the medical campus, all research protocols must be submitted to the BU/BMC IRB using the INSPIR system found on the INSPIR website <https://braan.bumc.bu.edu/brainlogin.asp>. The BU/BMC IRB does not review research proposals that are not submitted via the INSPIR system (except some of those that are to be reviewed by an external IRB). On the Charles River Campus, investigators submit protocols using either of the New Application forms (www.bu.edu/irb).

Protocols submitted to the BU/BMC IRB to be reviewed by WIRB must be submitted on the BU/BMC WIRB application found on the BU/BMC website. <http://www.bumc.bu.edu/irb/wirb/procedure/> . Investigators submitting protocols for review by WIRB on behalf of BU/BMC must submit the necessary pre-review documents to the BU/BMC IRB Office to allow for BU/BMC local context review. Instructions for submitting WIRB protocols and appropriate forms may be found at <http://www.bumc.bu.edu/irb/wirb/procedure/>. As a rule BU/BMC only allows industry sponsored, multi-centered research to be submitted to WIRB. The BU/BMC IRB retains the authority to determine whether each protocol may be submitted to WIRB or must be reviewed by the BU/BMC IRB.

Protocols submitted for NCI CIRB facilitated review must be submitted using specific SOPs developed for these reviews. Information about these processes is posted on the IRB website. [http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/WIRB%20or%20CIRB%20\(NCI%20or%20CDC\)%20%20INSPIR%20Instructions%2005-18-051.pdf](http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/WIRB%20or%20CIRB%20(NCI%20or%20CDC)%20%20INSPIR%20Instructions%2005-18-051.pdf)

Protocol Submission I

The IRB staff reviews the submission for completeness, asks the PI to submit any missing elements via an Administrative Modification memo or administrative deferral, and then make a preliminary determination as to whether the study is not considered human subjects research, qualifies as Exempt or whether IRB review can be expedited or must go to a convened full-board meeting for review.

For full-board reviews, protocols are assigned to next available panel agenda as appropriate based upon the panel expertise, and are made available to each panel member prior to the assigned meeting. Studies that meet the Expedited criteria are sent to one of the designated expeditors to be reviewed as soon as possible. Studies that are determined to meet the criteria for not human subject research or Exempt (per regulatory guidance) are reviewed and processed within the IRB office.

The following information must be included with the BU/BMC IRB application (when applicable). Not all of the information listed below may be required for all submissions (i.e. Exempt applications). Specific details about the requirements may be found on the applications on for med campus investigators on the website www.bumc.edu/irb under INSPIR instructions.

- Title of the study
- PI demographic information
- Information regarding all investigators (persons who will have access to research subjects or their study related identifiable data)
- Purpose of the study
- Funding sponsor of the study and the related grant application
- A complete study protocol. If a protocol is submitted for review and Panel members believe that there is insufficient information to enable an appropriate review, a request for additional information may be made to the PI.
- Results of previous research
- Subject inclusion/exclusion criteria
- A description of the research procedures to be performed
- A description of the study risks and how they will be minimized.
- A description of any expected benefits to be obtained from doing this research.
- Justification for use of any special/vulnerable subject populations and/or justification for exclusion of any particular groups
- Study design, including justification for the proposed sample size and an appropriate data analysis plan
- Description of procedures to be performed and identification of which ones are being done for research only

- The methods of identifying and contacting potential subjects (recruitment)
- The processes for obtaining informed consent, including setting, subject autonomy concerns, language interpretation issues, vulnerable populations issues, and justification for waiver of consent if a waiver is requested
- The procedures for documenting consent, including any procedures for obtaining assent from minors, using witnesses, justification for waiver of documentation of informed consent, translation of forms, and informed consent form storage
- Compensation to subjects for their participation, and justification
- Compensation for research-related injury
- Provisions for protection of subject's privacy, and confidentiality of data
- Extra costs to subjects for their participation in the study
- Extra costs to third party payers because of subject's participation
- A data safety monitoring plan (for studies that are greater than minimal risk)
- HIPAA information

Relevant Materials: The following items must be provided when applicable:

- Investigator's Brochure and/or Device Manual (when one exists)

A copy of the investigator brochure is available to all reviewers via the INSPIR system and a copy remains in INSPIR as an attachment to the research protocol

- Questionnaires, interview scripts, subject diaries, case report forms (CRFs), etc.

Documents that will be used by research staff to obtain information from subjects must be submitted with the application. These will be available to all reviewers via INSPIR.

- The Proposed Informed Consent Document

[See Section VIII for information related to Informed Consents](#)

- Research Advertising and Recruitment Materials

Any advertising or publicity information including recruitment letters, flyers, posters, public service announcements, newspaper, radio and television advertisements, and Internet content seeking study subjects for research that falls under the scope of authority of the BU/BMC IRB must be approved by the BU/BMC IRB.

These materials may be submitted by the PI to the IRB either with the initial application or subsequent to approval as an amendment. None of these materials may be used until IRB approval is obtained.

Recruitment materials are evaluated by the IRB for the following information, as applicable:

- A clear statement that this is research and not treatment
- A statement about the purpose of the research
- The eligibility criteria (summary form)
- Time commitments and other commitments for subjects
- The location of the research
- The name and telephone number or email address of a contact person or office
- The institution's logo (when appropriate)
- Any reimbursement or payments provided to subjects

Reimbursement information may be included in the recruitment materials with the following restrictions:

- An advertisement for subject recruitment may, if the investigator wishes, specify the amount of compensation by stating, "up to \$xxx"
- The amount of compensation may NOT be emphasized by using large, bold, underlined, italicized font or by putting this information first in the ad before the study purpose, procedures, and time commitment

Signatures Required

Department Chair

Each new IRB protocol must be signed off by a Department Chair or Section Chief. (On the Charles River Campus, if the PI of the study is a masters or doctoral student, then the protocol is signed by the faculty advisor rather than the department Chair.) On the med campus this process is done electronically using the INSPIR system, on the CRC the Department Chair signs a hard copy version of the IRB application. On the Certification/ Submission page of the INSPIR application the PI indicates who is responsible for signing off on his her protocol. Then when the PI submits the protocol it is automatically electronically routed for this Department Chair signature.

- It is the responsibility of the PI to know who is responsible for signing off on his/her protocols. If the PI does not know who should be signing his / her protocols, then he/she must contact his department administrator.
- If the PI is the Department Chair or Section Chief he/she CANNOT SIGN OFF ON HIS /HER OWN STUDY. The protocol has to be routed to the person designated to sign off on the PI's protocols, usually his/her supervisor (e.g., Dean).
- IF the Department Chair or Section Chief is a co-investigator on the study he/she may sign off on the protocol.
- All persons assigned to the Signature role may assign a proxy to sign protocols while they are away.

The following statement is part of the Department Chair's signature; Note to the Department Chair of this protocol: Each IRB application requires a department chair's signature. This signature indicates that the protocol is appropriate to be conducted in the department, that the PI has adequate expertise in the subject matter and in research, that the research staffing is appropriate, that the research will not interfere with patient care, that the standard of care described in the protocol reflects the standard of care in the department, and that the chair agrees that the research can and should be conducted within his/her department.

Other Signatures (Special Routing)

Certain types of protocols (e.g. those involving use of radiation or those involving the use of investigational drugs) require review and approval by one or more persons or committees prior to submission to the IRB. Those responsible for providing these sign-offs on protocols may approve, require modification or disapprove proposals. "Approvals" of this type do NOT constitute IRB approval, and all proposals must be reviewed by the IRB regardless of review by one or more of these persons or committees. Additionally, any modifications that are required by these reviewers must be reviewed and approved by the IRB.

On the medical campus, at the time that the PI completes his/her IRB application all appropriate Special Routing signatures are selected on the INSPIR Certification/ Submission page. The IRB office confirms that the protocols have received all the required reviews prior to approval of the protocol. In some instances, the Special Routing signature only indicates that that person or group is aware of the protocol and not that the protocol has been reviewed and approved by that committee (e.g. Human Gene Therapy Committee). Investigators are informed in the IRB approval letter that IRB approval does not constitute

approval by all other persons or Institutional committees and it is the responsibility of the PI to ensure that all necessary approvals have been obtained prior to beginning the study.

VIII. Informed Consent

Federal Regulations regarding Informed Consent

Federal regulations require that no investigator may involve a human being as a subject in non-research project without obtaining legally effective informed consent of the person or the person's legally authorized representative (LAR) unless the requirement for informed consent has been waived by the IRB. The investigator must provide the prospective subject or the LAR sufficient opportunity to consider whether or not to participate in the research and must minimize the possibility to coercion or undue influence. The information that is given to the subject or LAR shall be in language understandable to the subject or LAR.

21 CFR 50.25(a) and 45 CFR 45.116 require that the elements of informed consent criteria be met. The required elements of informed consent have been incorporated into the consent form template that is found in Section Q of the INSPIR application.

Research protocols that are determined to be "not human subjects research" or "exempt" by the IRB are not required to meet all the federal requirements for informed consent. The BU/BMC IRB may require that the investigators notify potential subjects of certain elements of consent as part of the approval of an Exempt study.

All research protocols that require Expedited or Full Board review are required to have a consent process and consent forms that contain all of the elements of consent unless

- The IRB approves a waiver of consent for the protocol
- The IRB approves the waiver of certain elements of consent (including the requirement for documentation of consent) (see **Informed Consent Categories** below).

The IRB makes the final determination as to whether informed consent or any elements of informed consent (including documentation of informed consent) can be waived. This determination is documented in the meeting minutes (for full board studies) and /or in the approval letter or reviewer feedback.

If the investigator requests that the IRB approve the Waiver of any of the other required elements of informed consent, then the investigator should clearly indicate the elements to be waived and the justification in the application or in a separate note to the IRB. The IRB then makes a formal determination regarding the waiver of other required elements of informed consent.

The IRB may waive the requirement for use of the BU/BMC Informed consent format as appropriate. Consents that are reviewed by the BU/BMC IRB and the VA IRB but where subjects are enrolled and consented at the VA are not required to be submitted in the BU/BMC format. In these cases, the PI submits the VA consent forms as an attachment to the protocol application.

On the medical campus, any exceptions to the use of the INSPIR consent forms must be approved by the Director of the IRB, one of the IRB Chairs or an Expedited reviewer.

Elements of Informed Consent

The following are required elements in an informed consent form (ICF): [45CFR46.116](#) and [21 CFR 50.25](#)

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others that may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the IRB, the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, the sponsor (and others, as appropriate) may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and/or an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- When appropriate, a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
- When appropriate, anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- When appropriate, any additional costs to the subject that may result from participation in the research.
- When appropriate, the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- When appropriate, a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- When appropriate, the approximate number of subjects involved in the study.

The IRB staff reviews all informed consent documents as part of its review to ensure that all required elements are included in the ICF unless waived by the IRB.

Review of Informed Consent

The IRB reviewers and the IRB Analysts/ Coordinators review the informed consent form using an Informed Consent checklist of required and optional elements (45 CFR 46.116 and 21 CFR 50.25). Required modifications are sent to the investigator. The PI is required to make the required modifications and return the protocol with the attached consent forms. The modifications are then verified by the IRB staff. If the PI's changes to the consent do not represent simple concurrence with the Board's

requirements then the protocol is sent back to the Full Board for review.

Consent Validation

Once the study is approved, the consent form(s) is/are validated by the IRB office. The validated consent form contains, as part of the footer, the approval date for the study, the expiration date of the study/consent, and the Chair's or Expeditors initials.

All signed informed consent forms must be retained after the end of the study for a minimum of three years by the Principal Investigator. Some studies will require that all study documents be retained for a longer period of time. It is the responsibility of the investigator to be aware of all of the regulatory requirements for record retention for each study.

Consent forms are no longer valid once the expiration date has passed or if they have been replaced by a subsequent version of the consent document. It is the PI's responsibility to ensure that the correct version of the consent form is always used in the research. It is a violation of institutional policy and Federal regulations to use expired consent forms to enroll subjects.

Informed Consent Categories

Written Consent

Informed consent must be documented on a validated BU/BMC IRB approved consent form unless these requirements are specifically waived or modified by the IRB. The consent form (ICF) must be signed and dated by the subject or his/her legally authorized representative. The expiration date on the ICF is the last day of the current IRB approval. The date of the subject's signature on the ICF must be on or prior to the expiration date stamped on the ICF. The subject must be given a copy of the signed consent form, unless this requirement is specifically waived or modified by the IRB.

Waiver of Documentation of Consent

Federal regulations permit an IRB to waive the requirement for the PI to obtain a signed consent form for some or all subjects if the IRB finds and documents that either

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

The IRB can approve a waiver of documentation of consent for expedited or full board studies if the criteria are met. Waiver of documentation of consent is granted by the BU/BMC IRB on a case-by-case basis. It is not permitted except in those instances in which the above criteria apply. In cases in which the documentation requirement is waived, the IRB may require that the PI provides subjects with a written copy of the consent document. The rationale for requesting the waiver of documentation of consent must be justified in the application.

Waiver of Consent in Non-Emergency Research

The BU/BMC IRB can approve a request for waiver of the informed consent procedure either by the expedited or convened full board process. In order to qualify for waiver of informed consent the research study must fulfill **all** of the following (four) criteria

- The research must present no more than minimal risk of harm to subjects (see Appendix C for definition of minimal risk);
- The waiver will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver

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

Waiver of consent is allowed by the IRB on a case-by-case basis. The investigator must address all four of the criteria above in the application. IRB review (whether expedited or full board) must ensure that each protocol satisfies each of the above criteria. In instances where consent is waived, it is still essential that appropriate procedures for maintenance of confidentiality be described in the protocol.

Waiver of Consent for Emergency Research

Waiver of informed consent is not allowed for FDA regulated studies except as described in **Federal Register**, Vol. 61, pp. 51498-51531) at Title 21 CFR Part 50. The BU/BMC IRB reviews proposals to determine whether they meet the requirements described in <http://www.hhs.gov/ohrp/humansubjects/guidance/hcdc97-01.htm> and **Federal Register**, Vol. 61, pp. 51498-51531) at Title 21 CFR Part 50.

Informed Consent for Non-English Speakers

Long Form

Special issues arise in situations when the research subjects do not speak or read English. Federal regulations require that informed consent be presented “in language understandable to the subject” and be documented in writing. Whenever possible, the documentation must be in the form of an informed consent written in a language understandable to the subject that embodies all of the elements of informed consent.

The Principal Investigator is responsible for translation of the consent form if subjects expected to be enrolled are not fluent in written English. A completely translated copy of the informed consent done by a qualified translator must be submitted to the IRB. The investigator must submit along with the translated consent an Attestation Form completed by a second qualified translator verifying that the translated consent contains all of the required elements. The attestation form must include

- The qualifications of the translator
- The qualifications of the verifier who is verifying the translation
- A completed checklist with the signature of the verifier
- A copy of the attestation form and the complete attestation process can be found on the IRB website at <http://www.bumc.bu.edu/irb/irbguidance/short-consent-form-process/> .

Expedited review of these versions is done if the protocol and the full English language ICF have already been approved.

Short Form

In accordance with 45 CFR 46.117 (b) (2) and 21 CFR 50.27(b) (2), the BU/BMC IRB may allow the use of a short form written consent document.

Short form consents, for use with non-English speaking subjects or illiterate (non-English reading) subjects may only be used with specific IRB approval. Use of the written short form consent must include documentation stating that the required elements of informed consent have been presented orally to the subject or his/her legally authorized representative (LAR) in their language.

Expedited review of the short form is allowed if the protocol, the full English language version of the ICF, and the English version of the short form document have already been approved by the IRB. The IRB must approve a written summary of what will be said to the subject or the LAR.

A copy of the summary (English version of ICF) along with a copy of the short form in the subject’s own language must be given to the subject or LAR.

Click here for SOP regarding the Short Form Consent Process

IX. Special Populations

Federal regulations require that special consideration be given to protecting the welfare of particularly vulnerable subjects. In general the regulations allow approval of research that is of minimal risk or that will benefit these subjects directly. However, the regulations require special safeguards, particularly with respect to obtaining informed consent.

Children

Children are defined as persons “who have not attained the legal age for consent to treatments or procedures involved in the research”. The BU/BMC IRB generally considers all subjects under the age of 18 as children. (Note: for NIH sponsored research, research subjects are considered children until they reach the age of 21.)

All studies which involve, or will potentially involve children must be identified by the PI at the time of submission of a protocol to the IRB. If children are to be added as study subjects after initial IRB approval, then the PI must submit an amendment describing how the children will be involved in the research and the potential risks to these subjects.

In all protocols involving children as subjects, the research must be classified into one of the four following categories. For those studies, the IRB approval letter and meeting minutes reflect the category under which the protocol was approved together with the protocol specific findings which justify application of that category.

The four categories of research involving children are based on degree of risk and benefit to the individual subjects;

- **Category 1:** Research involves no greater than minimal risk. (see Appendix C for definition of minimal risk)
- **Category 2:** Research involves greater than minimal risk but presents the prospect of direct benefit to the individual subjects. Category 2 can only be approved if (1) the risk is justified by the anticipated benefit to the subjects **and** (2) the relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches
- **Category 3:** Research involves greater than minimal risk with no prospect of direct benefit to individual subjects. Category 3 research can only be approved if (1) the risk represents a minor increase over minimal risk; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations; **and** (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding of the subject’s condition
- **Category 4:** Research that does not fall into one of the three above categories, but which the IRB determines presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Research in this category cannot be approved by the IRB without the approval of the Secretary of HHS.

Only research in Category 1 can be approved by the Expedited Review process since research must present *no more than minimal risk* to qualify for Expedited Review.

Assent and Permission

For research involving children as subjects the IRB must ensure that the study includes procedures for obtaining the assent of the child, if appropriate, as well as the permission (consent) of the parent(s) or legal guardian(s).

Assent refers to the child's agreement and must be solicited when the IRB determines if a child is capable of providing assent. As a general rule the BU/BMC IRB does not usually require assent for children less than seven years old, requires verbal consent only for children ages seven to eleven and requires written assent for children twelve and above. This determination is made however on a case by case basis depending all of the aspects of the study.

To make its determination regarding assent the IRB takes into account the ages, maturity, and psychological state of the children involved. If the IRB determines that the capability of some or all of the children 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 of 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.

To elicit assent the child must be provided with a fair explanation of what participation involves. Children with reading skills sufficient to understand the consent form may be invited to sign the form. Rarely the IRB will allow the child to assent by signing an assent signature line on the parental consent. Most frequently the IRB requires a separate assent form written in language appropriate for the child's age.

Consent of pregnant minors

In some instances a minor is legally allowed to consent on his/her own behalf without parental involvement. One example of this would be a pregnant minor, who has been independently making treatment decisions for herself, may be allowed to consent to research without the permission of her parent(s). This determination is made by the IRB on a case by case basis.

Permission

As part of its review the IRB determines whether the permission of one parent or two parents (or legal guardians) is required. For Categories 1 & 2, the permission of one parent is usually sufficient (although the IRB may, at its discretion, require the signature of both parents). For Categories 3 & 4 the permission of two parents is required (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child).

Prisoners

Federal regulations (45 CFR 46 Subpart C) require that an IRB must be constituted with at least one member who participates in reviews who is a prisoner or prisoner representative in order for the IRB to review research involving prisoners as subjects. The BU/BMC IRB currently has a board member who is a qualified prisoner representative. This "prisoner representative" is registered with OHRP as a prisoner representative per the OHRP requirements.

The investigator must clearly indicate in the IRB application that it is his/her intent to enroll subjects who are prisoners or who meet the federal definition of an incarcerated subject and are considered to require the special protections afforded to prisoners participating in research.

During the convened IRB meeting the Prisoner Representative serves as one of the reviewers for the study. The board votes on the protocol and votes on each of the criteria listed in Subpart C of 45 CFR 46. The results of the vote are documented in the IRB meeting minutes. The research proposals and the IRB's findings are sent to OHRP for review per their requirements. No research activities involving prisoners may be started until full approval has been obtained from the IRB.

Pregnant Women, Fetuses, or Neonates

Approval Criteria

Review of research involving pregnant women, human fetuses, or neonates must include the following:

- Where scientifically appropriate, preclinical studies (including animal studies or non-pregnant women studies) to provide risk assessment data for pregnant women and fetuses
- Prospect of benefit
 1. the sole cause of fetal risk is intervention or procedures that hold out prospect of direct benefit for the woman or the fetus
 2. If no prospect of benefit than the risk to the fetus must not be greater than minimal AND the purpose is development of important biomedical knowledge which cannot be obtained by any other means
 3. any risk is the least possible for achieving the objectives of the research

The IRB reviews research that involves pregnant women (does not exclude pregnant women) based on the criteria in Subpart B.

Informed Consent

Maternal Consent

- Research holds out prospect of direct benefit for the **woman or the fetus**
- Research holds out prospect of direct benefit for **both woman and fetus**
- No prospect of direct benefit to either woman or fetus; risk to fetus is not greater than minimal; purpose of the research is development of important biomedical knowledge that cannot be obtained by any other means

Maternal AND Paternal Consent

- Research holds out prospect of benefit solely to the fetus
- Paternal consent not required if father unable to consent because of unavailability, incompetence, temporary incapacity or pregnancy resulted from rape or incest

Pregnant Children

- Permission and assent is required as in Subpart D (Children's Regulations)
- The IRB determines whether a pregnant minor may consent for herself. Consideration is given as to whether the pregnant minor has been making her own clinical decisions (independent of parents or guardians).

Other Informed Consent Requirements

- No inducements, monetary or otherwise may be offered to terminate the pregnancy.
- Individuals engaged in research must have no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy.
- Individuals involved in the research must have no part in determining the viability of a neonate.

Research Involving Neonates

Neonates of Uncertain Viability and Nonviable Neonates: Approval Criteria

- Where appropriate, preclinical studies (including animal studies or non-pregnant women studies) to provide risk assessment data for neonates
- Consenting individual is fully informed about reasonably foreseeable impact of research on the neonate
- Individuals engaged in research have no part in viability determination
- Following additional rules applicable to each viability category

Neonates of Uncertain Viability

The conditions for research prior to viability determination are that the IRB must find

- That the research holds out prospect of enhancing probability of survival to viability with least possible risk to achieve that objective **OR**
- The purpose of research is development of important biomedical knowledge not obtainable by other means and there is no added risk to the neonate
- The informed consent is obtained from either parent or parent's legally authorized representative (with rape/incest exception)

Nonviable Neonates

The conditions for research in nonviable neonates are

- Vital functions are not artificially maintained
- Research will not terminate heartbeat or respiration
- No added risk to the neonate results from research
- The purpose is to develop important biomedical knowledge not obtainable by other means
- The informed consent is obtained from both parents except if one parent is unavailable, incompetent, or temporarily incapacitated; the father's consent is not required for pregnancy from rape/incest; 46.116 © and (d) waiver/ alteration is NOT applicable; legally authorized representative of either or both parents is NOT sufficient

After Delivery Research on Placenta, Dead Fetus, or Fetal Material

- Other Federal, State, or local laws
- Research subjects: individuals identifiable through information associated with after delivery placenta, dead fetus, or fetal material, directly or indirectly through linkers.

BU/BMC has special requirements for pregnancy testing prior to enrolling women of childbearing potential (including adolescents) in studies that involve MRIs done for research purposes (not clinical care). The policy is posted under IRB guidance on the IRB website.

Decisionally Impaired Persons

The use of decisionally impaired persons as research subjects presents a risk that their disability may compromise their capacity to understand the information presented during the consent process and their ability to make a sound decision as to whether to participate in the research. For this reason the BU/BMC IRB may make additional requirements to ensure protection of these subjects.

The BU/BMC IRB determines on a case-by-case basis whether subjects are required to consent for themselves or whether consent may be obtained from a Legally Authorized Representative (LAR). <http://www.bumc.bu.edu/irb/irbguidance/consentingdecisionallyimp/>. The BU/BMC IRB uses an algorithm <http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/Flowchart.decision.impaired.3.pdf> for guidance in determining whether consent by LAR is appropriate. Exceptions to the guidelines in the algorithm are made by the IRB on a case-by-case basis when the reason is well justified by the investigator.

Legally Authorized Representative (LAR): When the IRB approves for consent to be obtained from a subject's LAR consent of the following representative will be allowed:

- Court appointed guardian- in some instances a court may appoint a guardian who has authority to make decisions on behalf of a decisionally impaired person
- Research proxy: a person designated by the subject as a research proxy by durable power of attorney **prior to the subject becoming decisionally impaired**. The research proxy is specifically designated to make **research** decisions for the subject.
- Next of kin: when the subject has not appointed a research proxy prior to becoming decisionally impaired the IRB may allow the subject's next of kin to serve as the LAR to consent for research. The study records must clearly document how the next of kin determination was made. <http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/Legally%20Authorized%20Representative%20-%20Table.pdf> is a chart to be used to determine who is the next of kin.

***A durable power of attorney, healthcare proxy or "living will" does NOT automatically make someone eligible to make research decisions on behalf of a subject / serve as the research proxy.

Students, Trainees (e.g.: medical residents), and Employees

The BU/BMC IRB aims to ensure that a subject's decision to participate in research is truly **voluntary** and that there is no coercion for persons to participate in research. Students, medical residents, and

employees may be vulnerable to “subtle inducements to participate” in research by such methods as promises of academic rewards, professional achievement, vacation time, etc. Therefore, the BU/BMC IRB requires that additional protections be in place in research studies where these persons will be targeted for recruitment.

Generally, PIs who intend to recruit students, others in training status, or employees, as subjects are required to clearly define in their IRB application the subjects to be enrolled, the rationale for their participation and the proposed method for their recruitment. Students and employees should not be the sole recruitment target unless the research objective is to study this population.

Students are permitted to enroll in research studies. Sometimes they are expected to participate as a research subject as a course requirement. In every circumstance when students are enrolled as subjects, special attention must be paid to assuring that participation is voluntary, that students do not feel coerced, and that they are confident that there will be no negative repercussions if they choose not to participate. **Appendix A** lists a number of guidelines that must be followed by investigators who enroll students as subjects.

On the Medical Campus, in addition to adhering to these guidelines, the PI must notify the the Dean from the applicable school of the proposed targeting of students for research. The Dean must formally approve the protocol prior to approval of the protocol by the IRB. The Chief Medical Officer of BMC must approve protocols targeting interns and residents.

Employees and students (including trainees, lab personnel, etc.) who directly report to the PI or any of the co-investigators are NOT allowed to participate in those research studies. Rare exceptions will only be made by the IRB on a case by case basis when the PI has provided sufficient justification. Due to the increased risk of loss of confidentiality, the PI must also explain in the protocol the methods to be used to protect these subjects' identities in the research data.

X. IRB Procedures for the Review of Protocols and Amendments

Conducting Initial and Continuing Review

The IRB, through its review of new protocols and its oversight of ongoing protocols, protects the safety of human research subjects by ensuring that in general the criteria under [45 CFR 46.111](#) and [21 CFR 56.111](#) are met. These criteria require that:

- The protocol is scientifically appropriate and the degree of risk to the human subjects is justifiable.
- Risks to subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risks, and whenever appropriate by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- The risks to subjects are reasonable in relation to anticipated benefits (if any) to subjects, the general public, and science, and the importance of the knowledge that may reasonably be expected to result. (In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.)
- Selection of subjects is equitable.
- Legally effective informed consent will be obtained from research subjects or legally authorized representative(s) and will be documented in accordance with applicable regulations.
- When appropriate, the research plan makes adequate provision for monitoring of the data

collected to ensure the safety of subjects.

- There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- Vulnerable populations are protected and that they are not being coerced, or otherwise taken advantage of. Vulnerable populations include those identified in 45 CFR 46.111 and 21 CFR 56.111, as well as any groups of subjects identified through knowledge of local research context.
- All changes to approved research protocols are promptly reported to the IRB and that all new procedures are not initiated without review and approval from the IRB except to eliminate apparent immediate hazard to human subjects under the existing protocol.
- Continuing review is scheduled at an interval based upon degree of risk and the risk/benefit analysis. The Continuing Review intervals are documented in the minutes, approval letter and IRB database.
- Serious Adverse Events and Unanticipated Problems involving risk to human subjects or others are reported to the IRB, and if applicable, to the sponsor, FDA, OHRP, or other appropriate regulatory agencies per their stated policies. The IRB promptly reports serious or continuing noncompliance with IRB requirements or federal regulations and any suspension or termination of research privileges to the Institutional Official and to the sponsor, FDA, OHRP or other appropriate regulatory agencies.

Types of Review

(Convened) Full Board Review

The IRB Analyst/Coordinator assigns the review of each new full board protocol to a primary and secondary reviewer. The IRB Chair or the IRB Director may assist the Analyst with this assignment of reviewers. The assignment is based upon expertise or familiarity with the subject of the protocol or the study populations as much as possible. The reviewers serve as the lead discussants and present a summary of the study to the Panel for discussion and vote during the regularly convened meeting.

For review of new applications all board members receive all of the information listed below. Primary and secondary reviewers conduct in-depth review of all pertinent documentation listed below (as appropriate for the study):

- A protocol summary in lay language and supplemental materials as needed. Information contained herein must be sufficient to address all of the criteria for approval of research [45 CFR 46.111 and 21 CFR 56.111]
- A proposed informed consent form
- All recruitment materials and scripts
- All survey instruments, questionnaires and interview scripts
- A complete sponsor's protocol
- Any relevant federal grant application or federal contract proposals
- Any relevant Investigator Brochures for investigational drugs, medical devices, or biologic agents

- Relevant HIPAA documents
- Any additional relevant information required to address criteria of approval
- A data safety monitoring plan (when applicable).

For full-board continuing reviews and amendments, a single reviewer system is used. All board members receive the Progress Report (protocol information, accrual information, accrual categories, adverse event information, subject complaints, amendment information, protocol deviations, a summary of unanticipated problems and protocol findings information), access to the currently approved protocol and consents, access to all archived versions of the protocol and consents, access to all memos and approval letters previously sent to the investigator, The reviewer serves as the lead discussant and presents a summary of the information to the Panel for discussion and vote during a regularly convened meeting.

Most repository research requires that initial review be conducted by the full Board/ convened IRB. Subsequent reviews may be conducted by expedited process unless the convened IRB determines that the protocol should remain a full board protocol.

Expedited Review

Expedited Review is conducted in accordance with the Federal Regulations. Expedited reviews of new protocols, amendments, and progress reports are only performed by designated Expeditors. An IRB Chair, Vice-Chair, the IRB Director, or an experienced Board Member or Alternate (including Experienced IRB Analysts and Coordinators) may be assigned the role of Expediter, in accordance with the criteria defined in the Federal Register Vol. 63 November 9, 1998 (<http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm>)/

Applications are eligible for an expedited review if they involve no more than minimal risk and the only involvement of human subjects is in one or more of the categories authorized in [45 CFR 46.110](#) and [21 CFR 56.110](#).

The Expediter exercises full IRB authority except he/she may not disapprove the research. The expedited review process is not used to circumvent the normal review process. IRB members are informed of research that was approved by Expedited Review via the IRB agenda.

Continuing reviews are conducted using the expedited review process if the protocol was originally reviewed using expedited review; if the protocol has not yet enrolled any subjects and no additional risks have been identified; if subject accrual is permanently closed, intervention is complete, and the remaining research is limited to long-term follow-up; or if remaining research activities are limited to data review and analysis.

When conducting an expedited continuing review, the Expediter receives and reviews the full protocol including any modifications previously approved by the IRB, informed consent form, the Progress Report (which includes the number of subjects recruited, summary of any adverse events, unanticipated problems, withdrawals and complaints since the last review).

The BU/BMC IRB does not routinely use subcommittees for reviews. Special-expertise subcommittees are convened if deemed to be necessary by one of the Chairs or Vice-Chairs in collaboration with the IRB Director.

Exempt From Review

The federal Common Rule allows institutions to exempt certain categories of human research from full IRB review and adherence to the consent requirements under 45CFR46. In addition, some research activities are exempt because they do not meet the definition of “research” and/or do not involve “human

subjects.” At Charles River Campus, investigators submit studies they feel are exempt using the “:new Application Exempt Review”form. At the medical campus, investigators submit research involving humans to the IRB via INSPIR. The IRB then determines that the research is non-exempt or that the research is exempt from further BU/BMC IRB review because

- It does not meet the definition of human subject research
- It fits a categorical exemption as described in 45 CFR 46.101b (1-6)
- It is non-exempt human subjects research but BU/BMC is not engaged in the research or the responsibility for IRB review has been ceded (by agreement) to another registered IRB.

The IRB provides the investigator an “Exempt from further BU/BMC IRB Review” letter.

Information regarding Exempt research can be found at
<http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/Exempt%20slides.3.05.pdf>

Instructions regarding Exempt submissions can be found at
<http://www.bu.edu/cms/www.bumc.bu.edu/irb/files/PDFs/INPIR%20exempt.instruct.3.051.pdf>

Categorical Exemption Criteria:

Research activities in which the only involvement of human subjects will be in one or more of the following categories are eligible for exemption. **[The categorical exemptions do not apply to research involving prisoners, pregnant women, human fetuses, or neonates]:**

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as

(i) research on regular and special education instructional strategies, or

(ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures **[does not apply to children]**, interview procedures **[does not apply to children]** or observation of public behavior **[only applies to research with children when the investigator(s) do not participate in the activities being observed]**, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2) of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

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

OHRP interprets “existing” as follows:

To qualify for this exemption the data, documents, records, or specimens **must be in existence before the project begins**. Following is the edited version of an example given by OHRP. An investigator wants to screen blood samples at a hospital for incidence of HIV by using specimens that were drawn for some other purpose but remain in the hospital laboratory. If the investigator proposes to use specimens that had been drawn prior to the initiation of the research and are, for some reason, "on the shelf," the protocol will qualify as exempt if the other requirements of (4) are met (i.e., the sources are either publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects). If the specimens will be drawn after the start date of the project, the protocol is not exempt from IRB review, even though the specimens will be drawn for purposes other than the research, and the research is only using excess blood. The latter protocol may, however, qualify for expedited review.

(5) Research and demonstration projects which are conducted by or subject to the approval of U.S. Federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

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

To qualify for this category, studies must also meet the following additional criteria:

- The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
- The research or demonstration project must be conducted pursuant to specific federal statutory authority.
- There must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB).
- The project must not involve significant physical invasions or intrusions upon the privacy of participants.

(6) Taste and food quality evaluation and consumer acceptance studies,

(i) if wholesome foods without additives are consumed or

(ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Review of Protocols for Determination of Exemption

An experienced IRB staff person performs administrative review of the Exempt submission to determine whether the criteria have been satisfied. In some cases a second experienced reviewer or a board member also reviews the submission. During this review period protocols may be sent back to investigators to obtain additional information necessary to make the determination. If it is determined that the study meets the Exempt criteria, an “Exempt from further IRB Review” letter is provided to the PI. So that the institution can verify that the research activities remain within the bounds of the exempt category, investigators are informed in their Exempt letter that they must resubmit their exempt application if any changes are necessary.

Exempt Because Human Subjects Are Not Involved

Research that does not involve human subjects is also exempt from IRB review.

A human subject is “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.” The regulations provide further that “private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.” In some cases the “readily ascertainable” standard can be met because disclosure of identifiers is prohibited by law, such as a state data source or archive where a law would prohibit the release of identifiers. Alternatively data obtained from a repository can also be determined to have met the standard if the following conditions are met: 1) there is a restrictive written agreement between the repository and the recipient that prevents disclosure of identifiers to the recipient; and 2) the repository was established under the oversight of an IRB with an OHRP FWA and in accordance with OHRP guidelines. Please note that the criteria for identifiability under the Common Rule and HIPAA are not totally congruent. Thus, a study of HIPAA de-identified data may still constitute human subjects research.

Exempt Because the Activity Does Not Meet Definition of Research

The common rule defines research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” Quality assurance projects or public health surveillance activities typically fall into this category; if these projects or activities are not intended to develop or contribute to generalizable knowledge, then they do not meet the definition of research. The IRB does not require an application for this type of activity, unless it meets the definition of research. Frequently protocols may be determined to represent quality assurance AND research. In such cases IRB review is required.

If an investigator requires a determination by the IRB to verify that a proposed activity fits within these (not human subject research) categories he/she must submit an application that contains sufficient description of the activity so that the IRB can make an appropriate determination. Any determination rendered applies solely to the activity described and not to subsequent alterations. A description of the modified application is posted on the IRB website (www.bumc.bu.edu/irb).

Review Decisions

The BU/BMC follows the regulations under 45 CFR 46 and its subparts (and 21 CFR Parts 50 and 56 when applicable) in its review of all human subjects research.

The IRB may vote to approve, conditionally approve, defer, or disapprove all research activities. During convened meetings this is done by the following process

- All persons with a conflict of interest are required to leave the room before final discussion and a vote is called
- A board member makes a motion to approve, conditionally approve, defer or disapprove a research protocol or action
- Another board member seconds the motion. (If no one seconds the motion then the motion dies without a vote).
- If the motion is seconded then the Chair calls for a vote on the motion that is on the table
- For the motion to pass it must be agreed upon by a majority of the voting members present (including those who abstain and those who recuse themselves unless those who recuse are replaced by appropriate alternates)

Approval indicates that the protocol or action has been approved as submitted requiring no changes, additions, or modifications.

Conditional Approval indicates that only minor clarifications to the required elements under 45 CFR 46.111 and 21 CFR 56.111 are required in the submission and revisions require only simple concurrence by the investigator.

The IRB Chair or the Chair's designee may subsequently approve on behalf of the IRB under an expedited process a research protocol that has been revised in response to a conditional approval (i.e., where revisions require only simple concurrence by the investigator and the investigator concurs).

With a conditional approval, the PI must respond specifically to each IRB comment point by point within 60 days or the proposal will be removed from consideration.

In extenuating circumstances, the PI may request from the IRB Chair or the IRB Director an extension to the 60 day submission deadline for revisions to conditional approvals. These extensions are granted on a case by case basis and do NOT represent extensions in IRB approval beyond the study expiration date.

Deferral The IRB defers approval when the panel requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly related to the requirements under 45 CFR 46.111 and when the revisions cannot be met by simple concurrence. A subsequent review by the convened IRB of the complete protocol with the revised material is necessary to determine approval. If an IRB application is deferred, the revised submission must be reviewed by the full board.

With a deferral, the PI must respond in writing specifically to each IRB comment point by point. If the revisions requested by the IRB are not received within 60 days after the date of the IRB notification the proposal will be removed from consideration.

In extenuating circumstances, the PI may submit a written request to the IRB for an extension to the 60 day submission deadline for revisions to conditional approvals.

Disapproval indicates that the IRB has found major flaws in the design of the research, or other problems so great, that they determine that the study must be redesigned to address the issues. In this case, a new application must be submitted with the re-designed study. Protocols cannot be disapproved by the expedited process; they must be reviewed by a convened full board. Investigators whose protocols are disapproved may appeal this decision by responding in writing, and may request an opportunity to appear before the IRB.

Determining Studies That Require Review More Often Than Annually

The IRB conducts review of research at intervals appropriate to the degree of risk, but at least once per year. Continuing Review is required as long as the research remains active for long-term follow-up of subjects. Continuing Review is also required when the remaining research activities are limited to data analysis. Progress Reports are no longer required once the data analysis is complete and the study question has been answered. At this point a final report is submitted by the PI to the IRB and the study is closed. Investigators are required to submit a final report to close out their studies rather than just allowing their studies to expire.

The IRB may determine that certain studies must be reviewed more often than once a year based upon the initial review or continuing review (e.g. 3 months, 6 months, 9 months, or 12 months). Additionally, the IRB may require review after a predetermined number of subjects have been enrolled into the protocol. The IRB minutes document the specific review interval, as does the IRB approval letter.

Studies that might be considered for review more frequently than once per year include, but are not limited to:

- The use of vulnerable populations, including those identified in [45 CFR 46.111\(b\)](#) and [21 CFR 56.111\(b\)](#) as well as cognitively impaired persons or others determined to be vulnerable by the IRB
- The withdrawal of standard treatment or therapy regardless of replacement by experimental treatment, when there is a high risk of mortality or morbidity
- Significant risks or potential serious impairment to the subject
- Risk when there is no potential clinical benefit to the subject
- Invasive surgical procedures
- Gene transfer research
- Phase I studies
- Research by investigators who have required corrective action in previous studies

Notification of Investigators WHAT DOES THIS “NOTIFICATION” REFER TO?

The IRB promptly reports all findings and actions to the Principal Investigator including requests for additional information, all IRB determinations and acknowledgment of notifications received.

Record of IRB determinations and communications are maintained in permanent study files located in the IRB office and, for the med campus, after March 15, 2004 in the INSPIR system. After the close of the study, files are maintained for a minimum of three years, or longer if required for a particular study either in the IRB office or in an off site secure records storage facility. Communications submitted to the IRB via INSPIR after March 15, 2004 are stored electronically in the INSPIR system and on a backup server maintained by the BU/BMC OIT department.

The IRB Approval Letter includes the following information about approval and conditions of approval:

1. Study protocol name (with version number and/or date)
2. Notice of approval
3. Date of approval
4. The date any final revisions were reviewed and approved by the IRB
5. Expiration date (which is not more than one year from the approval date)
6. A statement that no modifications are to be made without prior IRB approval
7. A statement that the IRB must review all recruitment materials before they can be used
8. The requirements to report all unanticipated problems, amendments/modifications to the protocol, protocol deviations, or study termination to the IRB in a timely manner.
9. Continuing review requirements
10. Notice that the protocol may be audited at any time
11. Requirement to retain study-related documents (including informed consent forms and protocol) for at least 3 years after the completion of the study.

Approval letters are made available to the Principal Investigator and all those members of the research protocols who have been assigned read only or read/write privileges within INSPIR. If required the IRB reports its findings/actions to a sponsor or regulatory agency.

Investigator’s Right to Appeal

If an IRB application is disapproved, the reasons for disapproval are conveyed to the investigator via INSPIR. The investigator has 30 days to make a formal request to the IRB to reconsider by responding to the disapproval letter within the INSPIR system in writing. The investigator may request an opportunity to appear before the IRB to discuss the issues addressed in the disapproval.

XI. Compliance Oversight of Research

Quality Assurance Audits of Research

The IRB has the responsibility to oversee the conduct of research that it approves. Consistent with this responsibility, the IRB may audit research studies at BU/BMC or studies in which faculty and/or staff of BU/BMC is engaged in research outside the institution. The IRB also has the authority to observe, or have a third party observe, the informed consent process of research it has approved, and to verify that the study is being conducted as required by the IRB and within the Institutional policies and procedures and site-specific procedures, as appropriate. The IRB staff, Board Members or members of the Office of Clinical Research Resources may perform site visits or use another party, either affiliated or not affiliated with the institution, to verify information in the study application, or in an interim or continuing review report. Other means of verification may include queries to the PI or other members of the study staff, review of sponsor's monitoring reports and DSMB reports, queries to subjects, family members or clinicians. The IRB may request signed copies of informed consents or other documents and may conduct interviews with screened or enrolled subjects as deemed necessary to verify investigator compliance.

The Manager of Research Quality Assurance is the person primarily responsible conducting IRB audits at BU/BMC. The Manager of Research Quality Assurance reports administratively the Director of the Clinical Research Resources Office as designated by the Director of the Office of Clinical Research. The Manager of Research Quality Assurance has accountability to the Panel Chairs for the research audits.

Protocols may be selected randomly for audit or may be targeted for audit at the discretion of the Board Chairs and IRB Director in Collaboration with the Institutional Official. Situations that may warrant a targeted audit include, but are not limited to:

- A study conducted by an investigator who previously failed to comply with federal regulations or IRB policies
- Complex projects involving unusual levels or types of risk to subjects
- Studies conducted at an off campus site including international research
- Projects where continuing review information suggests that possible material changes occurred without IRB approval
- Studies not otherwise monitored (e.g.; single center, investigator initiated, unfunded, etc)
- Locally (BU/BMC) manufactured drug, biologic, or device
- Investigator-held IND or IDE
- Studies with SAEs of major concern or a large number of SAEs
- Studies where concerns have been identified by the DSMB, DMC or study monitors
- Studies with unusual subject complaints
- Gene transfer research
- Investigator or research staff financial conflict of interest
- Institutional financial conflict of interest

During the course of an IRB audit information is gathered from IRB records, the investigator study records, source documents (such as the subjects' clinical records) and the sponsor's files. Information may also be gathered from multiple additional sources including, but not limited to;

- Incident reports
- Radiation safety or source documents
- Families of research subjects
- Research staff
- Research subjects
- Research subject surrogates
- Sponsors

Audit reports: Reports of audits are presented to the convened IRB by the Auditor. At the time of the presentation the IRB votes to either, accept the auditor report, request additional information, or not accept the audit report. Secondly, the IRB votes to approve the investigators corrective action plan (CAP), request changes to the plan, or disapprove the CAP. These votes are captured in the IRB minutes.

Non-Compliance

As a result of an IRB audit, or in the course of routine IRB business, incidents of noncompliance by investigators with federal regulations or BU/BMC IRB policies may be identified. When these situations occur they are brought to the attention of the Panel Chair. The incidents of non-compliance are then reviewed and managed in one of several ways depending on the severity of the non-compliance and the determination as to the willfulness of the investigator. For each incident of non-compliance that is identified a plan of correction is documented. Further audit may be required. In order to assess subject risk, the IRB may also seek additional expertise or supervision. When the IRB identifies issues of serious or continuing non-compliance a report is made to OHRP, the FDA (when applicable), the Institutional Official, the PI's department Chair and the sponsor by the IRB Director (designated Human Protections Administrator on the FWA). If the Board Chairs or the IRB Executive Committee determine that there are concerns regarding investigator non-compliance these are brought to the attention of the IO/Director of the Office of Clinical Research who may refer them to other institutional officials for review.

Protocol Deviations

Investigators are required to report protocol deviations to the IRB as soon as they occur or as soon as the investigator becomes aware that they occurred. Protocol deviations are summarized and reported to the IRB. As part of each Progress Report the IRB reviewers are able to see all protocol deviations which have been reported. Protocol deviations are processed by the IRB staff, in collaboration with the Manager of Research Quality Assurance, the IRB Chairs or the IRB Director when applicable. Protocol deviations are acknowledged when it has been determined that the Corrective Action Plan (CAP) is appropriate.

The IRB staff collaborates with the IRB Chair as appropriate to determine which protocol deviations require review by the convened IRB Panel. Those protocol deviations deemed to represent serious risk to subjects or others are reviewed by the convened IRB Panel.

Discrepancies in Application of Policies or Regulations

The Executive Committee plays a central role in reconciling non-willful discrepancies in the application of policies or regulations. When such discrepancies are discovered, an inquiry into the situation is initiated. This inquiry is reviewed by the Chair or Vice Chair. The inquiry may include a meeting with the investigator. A corrective action plan is developed and presented to the Executive Committee for discussion and ratification. Revisions to the plan are made as needed. The final plan is then presented and approved by the IRB Panel prior to allowing the investigator to apply the corrective action plan.

Serious or Continuing Noncompliance

Serious or continuing noncompliance refers specifically to compliance with 45 CFR part 46, 21 CFR parts 50 and 56 or the requirements of the Institution. The IRB may become aware of possible serious or continuing noncompliance in several ways, including

- **In conducting protocol reviews or reviews of progress reports and amendments**
- as a result of a self-report by an investigator
- from a report from another investigator or clinician
- a complaint from a subject or subject's family
- through an audit (either by IRB auditor or by an auditor representing a sponsor or agency)
- or from a "whistleblower."

When incidents of potential serious or continuing non-compliance are identified, it is the decision of the Panel Chair to

- Decide whether the study should be suspended, AND
- Refer the matter to the IRB Manager of Research Quality Assurance (IRB Auditor) to investigate the evidence as to whether serious or continuing noncompliance has occurred. Evidence can include, but is not limited to, study records and data, interviews with the PI, research team, and study subjects.
- If at any point during the investigation the weight of evidence indicates that serious or continuing noncompliance is likely and/or that study subjects are at risk if the study were to continue, the IRB may suspend the study until the end of the investigation.

The IRB Chairs, IRB Director, or Institutional Office may request an audit of any research protocols suspected of noncompliance. The auditor then reports his/her findings to the IRB Chair, IRB Director and IO and subsequently the IRB Chair determines whether the report should be submitted to the convened IRB Panel. The Principal Investigator is notified in writing of IRB concerns, and is expected to respond, point by point to the concerns in writing.

At the conclusion of a sufficient investigation, the IRB Director notifies the IO of the outcome specifying whether noncompliance had occurred, and if it did, the nature of that noncompliance. For research covered under the institution's FWA, if the findings meet the requirements for incident reporting, http://www.hhs.gov/ohrp/policy/incidreport_ohrp.html, the IRB Director submits a report of the incident to OHRP. A copy of the report is provided to the PI, the Institutional Official, the PI's Department Chair, and Sponsor/Grantor, the appropriate BU/BMC grants office, the Board Chair(s), and if appropriate, the FDA.. The report describes the IRB action in response to the findings including dismissal of the concern or allegation, study suspension or study termination; any corrective action plan; or IRB monitoring plan for preventing future noncompliance

Suspension or Termination of IRB Approval

The IRB may vote to restrict, suspend or terminate an investigator's privilege to conduct a research study if it finds that research activities are continually (either purposefully or through careless disregard) not being conducted in accordance with federal regulations, state law, or institutional policies governing human research. Any suspension or termination of approval to conduct a research study is conveyed to the Principal Investigator in writing and includes a statement of the reasons for the action. The PI may appeal this decision by submitting an appeal in writing to the Chair within 30 days

If the study is suspended or terminated, IRB Director notifies the Institutional Official, the PI, and the PI's Department Chair within 2 working days of the decision. The suspension or termination notice includes a statement of the reasons for the action. If required under the terms of the FWA, the IRB Director sends a preliminary notification of the study suspension/termination to OHRP and sends copies to the IO, the Sponsor/Grantor, the BU/BMC grants office, the PI's department Chair/Section Chief, and the FDA (if applicable). This notification occurs within 5 working days. Reporting to OHRP may be done in several steps; a preliminary report may be submitted and then, once the final corrective action plan has been agreed upon with the investigators and reviewed and approved by the IRB a final report may be completed.

Any allegations of [research misconduct](#) are referred to the Dean of the appropriate institution as described in the [Boston University policy](#) or as provided in the Boston Medical Center Research Misconduct Policy.

XII. Special Topics

Investigational New Drug (IND)

Any research involving a drug, whether FDA approved or not, requires IRB approval. Drugs or drug combinations which have not been approved by the FDA may require an IND number from the FDA. The IND number and the name of the IND sponsor must be clearly indicated on the application.

Approved drugs being studied for an off label use such as an unapproved indication, for use in a different population, or used in a different dose or route than approved require either an IND from the FDA, IRB approval of the research as being IND Exempt under 21 CFR 312.2 (b), or documentation from the FDA stating that the drug or drug combination is IND Exempt.

Studies involving off label use where the investigator requests that the IRB approve an IND Exemption must meet all of the following criteria of 21 CFR 312.2:

- (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
- (v) The investigation is conducted in compliance with the requirements of Sec. 312.7.

Items (i) and (ii) on the above list are attested to by the PI in the application. The PI must provide to the IRB, as part of the protocol submission, sufficient documentation to support item (iii) above. This information may include the results of previous studies, including animal and other human studies, discussion of risks, indications for populations who might be at increased risk, etc. This information must be included as an attachment.

During a convened meeting the IRB will determine whether the 312.2 criteria have been met. After review, the IRB may determine that the data presented do not substantiate an IND Exemption or the IRB may require that the investigator consult with the FDA and obtain a written determination about whether the study will require an IND.

Although the investigator makes a provisional determination that the 312.2 exemption applies, the IRB has regulatory responsibility to review and approve the conduct of a study under the 312.2 exemption. The basis for the IRB's determination will be included in the IRB meeting minutes. The investigator is informed of the finding in the IRB approval letter. The IRB may inform other departments within the institution, including the Office of Research Administration, BMC Grants and Contracts, the BU/BMC Office of Clinical Research Resources of its determinations.

Some research protocols may involve food products, food supplements or other products that are being studied that are making claims that may cause them to come under FDA's new drug regulations (i.e. making a "drug claim" or "having an effect on a disease".) Where the IRB does not receive sufficient documentation that a product is being used with claims permitted by FDA regulations, the IRB may either consult the FDA or require an investigator to provide written documentation from the FDA about the regulatory status of the product being used in the study.

Investigational Device Exemption (IDE)

Any research involving a device, whether FDA approved or not, requires IRB approval.

Significant vs. Non-significant Devices: A significant risk (SR) device means an investigational device that presents a potential for serious risk to the health, safety, or welfare of a subject and

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

Devices which are not approved by the FDA or which are being studied for "off-label uses* require an IDE from the FDA, an IRB deemed IDE under 21 CFR 812.2 (non-significant risk device /NSR determination), or documentation from the FDA stating that the device is a non-significant risk (NSR) device.

For device studies with an IDE from the FDA, the IDE number must be clearly indicated on the INSPiR application in Section P with the name of the IDE sponsor (the person or company which holds the IDE.)

If the investigator is requesting that the IRB make a NSR (non-significant risk device) determination under 812.2, then as part of the protocol submission, it is the responsibility of the PI to provide to the IRB sufficient documentation to support the claim that the device, AS BEING USED IN A PARTICULAR STUDY, is a non-significant risk device. This information may include the results of previous studies, including animal and other human studies, discussion of risks, indications for populations who might be at increased risk, any information as to how the device has been altered, etc. This information must be included in the application.

It is the responsibility of the IRB to make determinations as to whether the research involves a significant risk or a non-significant risk device under 21 CFR 812.2. During a convened meeting the IRB will determine whether the 812.2 criteria have been met and the device is a NSR device. If the IRB determines that the 812.2 criteria have been met, the NSR determination is considered to be a "deemed IDE" and the investigator is considered to be the sponsor with abbreviated FDA reporting responsibilities as described in [21 CFR 812](#) unless some other company or individual is the regulatory sponsor.

If the IR determines that an IDE is required the IRB notifies the investigator and the sponsor. The investigator must then consult the FDA for a determination as to the device's regulatory status.

The IRB's determinations regarding NSR devices are documented in the IRB minutes. The investigator is informed of the IRB's findings in the IRB approval letter via INSPiR. The investigator provides the sponsor a copy of the letter. The IRB may inform other departments within the institution, including the Office of Research Administration, BMC Grants and Contracts, the BU/BMC Office of Clinical Research Resources of its determinations.

Emergency Use Notification and Reporting

Drugs and Biologics: The emergency use of an **investigational drug or biologic agent** with a patient 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 may occur if it is the medical judgment of a physician that it is in the patient's best interest. Any subsequent use of this test article is subject to IRB review and approval.

The physician must notify the IRB Chair or IRB Office prior to this emergency use, but this notification is not to be construed as IRB approval. The patient, or legally authorized representative in accordance with FDA regulations, must sign the consent form. This patient is not considered a research subject and data from this patient may not be included with the study data or in any report of the research. The physician

must submit a written report of this emergency use to the IRB within 5 working days.

Medical Devices: The emergency use of a medical device may occur if the patient is in a life-threatening condition that needs immediate treatment; there is no generally acceptable alternative for treating the patient and there is reason to believe that the medical device will provide a benefit; and because of the immediate need to use the device, there is no time to obtain IRB approval. The physician must notify the IRB Chair and FDA's Center for Devices and Radiologic Health prior to use of the device. These notifications are not to be construed as IRB approval. The patient, or legally authorized representative in accordance with FDA regulations, must sign a consent form. This patient is not considered a research subject and data from this patient may not be included in any report of the research. The physician must submit a written report of this emergency use to the IRB within 5 working days. Any subsequent use of this device is subject to IRB review and approval.

A medical device fitting the above procedure includes a device that does not yet have an IDE, or if the proposed use is not approved under an existing IDE, or if the physician or institution is not approved to use this device under an existing IDE.

Humanitarian Device Exemptions

Regulatory Background

The purpose of the HDE law and its implementing regulations ([21 C.F.R. Part 814](#)) "is, to the extent consistent with the protection of the public health and safety and with ethical standards, to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States." [21 C.F.R. §360j (m) (1)] The law prescribes a method that permits a manufacturer to lawfully market a device without meeting the efficacy standards generally required for FDA pre-market approval of devices. After a manufacturer applies for an HDE, meets the regulatory requirements¹, and obtains FDA approval of HUD status, the HUD may be used in humans. However, the law permits the use of HUDs only in facilities that have a local IRB and provided that the IRB approves the HUD's use in the facility.

HUD definition 21 U.S.C. §360j(m)(2)

- (A) the device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States,
- (B) the device would not be available to a person with a disease or condition referred to in subparagraph (A) unless the Secretary grants such an exemption and there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition, and
- (C) the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

Application of 21 C.F.R. §56.111 Approval Criteria

The BU/BMC IRB performs initial and continuing review of each HUD. For initial approval of a HUD, full board review is required; however, continuing review may take place under an expedited process.

The BU/BMC IRB may minimize or ignore certain approval criteria when evaluating a HUD at the discretion of the Panel and the Chair(s). Although the requirements of 21 C.F.R. Part 56, including continuing review apply, "an IRB evaluating a HUD retains the discretion to minimize or ignore approval

21 U.S.C. §360j(m)(2)

criteria that may be inappropriate in the treatment context (e.g., ‘the importance of the knowledge that may be expected to result’).” [61 Fed. Reg 33232, 33240]

The BU/BMC IRB follows the FDA Guidance for HUDs [\[Humanitarian Device Exemption \(HDE\) Regulation, Questions and Answers: Final Guidance for Industry\]](#) (July 12, 2001), Food and Drug Administration Center for Devices and Radiological Health] which states that the FDA does not interpret the HDE law to require IRB review and approval for each individual use of the HUD. Thus it states that the law permits “the IRB to approve the use of the device in general, use of the device for groups of patients meeting certain criteria, or use of the device under a treatment protocol.” [61 Fed. Reg 33232, 33235 (June 26, 1991)] The BU/BMC IRB requires that HUD protocols be submitted via INSPIR, be reviewed by the convened IRB and that progress reports be submitted at least annually. The progress report must indicate how many patients have been treated with the device and any adverse events or patient complaints related to the device. In addition, if it desires, “an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chair, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate.” .

Informed Consent

Since the HDE law does not require informed consent and because the FDA has determined that the humanitarian device exemption provides for temporary marketing approval, HUD use does not constitute “research” or an “investigation” which would normally require informed consent [61 Fed. Reg 33232, 33235 (June 26, 1991)]. However, the FDA does not intend for the HUD waiver from 21 C.F.R. Part 56 informed consent requirements to preempt institutional policies that require informed consent.

BMC policy requires written informed consent for the procedure in question unless immediate care is necessary to prevent jeopardy to the patient’s life, limb, or mental well being. The IRB can determine the exact form this informed consent will take and the IRB may require certain information be provided to patients as part of the consent process.

Importantly, it should be noted that if the manufacturer wants to collect safety and effectiveness data in support of a pre-market approval (PMA) application, the informed consent requirements under Part 56 would apply.

Emergency Use of a HUD

In an emergency, a physician can use a HUD prior to IRB approval if he or she determines that BU/BMC IRB approval “can not be obtained in time to prevent serious harm or death to a patient.” 21 U.S.C. §360j (m) (4) (B). In such a circumstance, the physician shall, after the use of the device, notify the chairperson of the BU/BMC of such use. Such notification shall include;

- the identification of the patient involved
- the date on which the device was used,
- and the reason for the use.

(Note: this notification is not necessary if the HUD is reviewed by the IRB prior to use.)

Off-Label Use of a HUD

In an emergency, a HUD may be used off-label, but FDA has stated that the emergency use rules for non-approved devices shall apply to HUDs. Namely, the physician should (if possible) seek prior concurrence of the IRB chairperson, informed consent, and an independent assessment from an uninvolved physician. Prior notice to the HDE holder is required. After the use, the physician must report to the HDE holder and to the IRB if not done previously.

[for more information see [Humanitarian Device Exemption \(HDE\) Regulation, Questions and Answers; Final Guidance for Industry](#) (July 12, 2001), Food and Drug Administration, Center for Devices and Radiological Health].

User Facility Adverse Event Reporting Requirements

BU/BMC has to report to either or both the FDA and the manufacturer.

Death Reported Directly to FDA: “Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to the death of a patient of the facility, the facility shall as soon as practicable, but not later than 10 work days after becoming aware of the information” it must report both the FDA and the manufacturer. 21 C.F.R. §803.30(a) (1)

Serious Injury Reported to Manufacturer: “Reports of serious injury. Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of the facility, the facility shall, as soon as practicable but not later than 10 work days after becoming aware of the information” must report to the manufacturer. 21 C.F.R. §803.30(a) (2) If the manufacturer is unknown, the report shall be made directly to FDA.

Appendix A. Guidelines for Enrolling BU Students as Research Subjects & Using Student Subject Pools

In some research situations, use of students is integral to a research protocol. This is particularly true of research into teaching methods, curricula and other areas related to the scholarship of teaching and learning. In the social and behavioral sciences course credit is commonly offered for research participation.

An underlying principle of the regulations governing use of human subjects in research is that the subject's participation is voluntary and based upon full and accurate information. The student-teacher relationship raises the issue of volunteer participation. Students may volunteer to participate in the belief that doing so will place them in a favorable situation with faculty (e.g., better grade, good recommendation, employment possibilities), or that failure to participate will negatively affect their relationship with the investigator or faculty (e.g. lower grade, less favorable recommendation, being "uncooperative and not part of the scientific community).

Care should be taken to eliminate or reduce the risk that undue influence of faculty or coercion affects student participation in research. The following guidelines are offered to assist BU departments and faculty who engage in research projects in which students will be asked to be research subjects:

- Students should be of the age of majority in the state of Massachusetts (18 years old). Research involving minors (under 18 years of age) as subjects, (16 or 17 year old college students) in most instances requires parental (or legal guardian) consent, as well as the assent of the student. Some types of research may qualify for a Waiver of consent (parental permission).
- Generally researchers may not access classroom performance evaluations, grades, and information in a (current) student's records without prior written permission from the student, regardless of the access an investigator may have in his/her academic role. (See FERPA information at <http://www.bu.edu/reg/ferpa/ferpa-policy.html>)
- When research activities to be done by the students are not part of the required class activities, the instructor should arrange to have the data collected by an independent third party, so that the instructor does not know who participated and does not have access to the identifiable data or identity of participants for any purpose until grades have been assigned and entered. For instructors using pre- and post- tests to determine efficacy of a particular curriculum, a colleague or third party should obtain the consent forms and distribute the tests when the instructor is not present (a graduate teaching assistant in the class in which the student/subject is enrolled does not qualify as a third party for collecting the data on behalf of the instructor).
- When course credit or extra credit is given to students who participate in research as part of a course requirement, students are to be given other options for fulfilling the research component, for example; short papers, special projects, book reports, and brief quizzes on additional readings, research seminars, or completing a similar project. **These projects must be comparable** in terms of time, effort and educational benefit to participation as a research subject to ensure that students are not being coerced into becoming subjects. Alternatives offered to student subjects need prior IRB approval. Departments seeking to use student subject pools and offering projects including pre-and/or post-testing also require IRB approval.
- Solicitation of volunteer student subjects for research must be done in a non-coercive manner. To avoid undue influence, subjects should be recruited by a general announcement, central posting or announcement mechanism and should include a clearly written description of the project and a statement of the proposed student participation. In addition to being provided with the traditional information and consent forms, the student should also be provided with the name and contact information of a neutral third party (the IRB at 617-358-6115 or irb@bu.edu) to contact should they feel coerced at any time during the process.

feel coerced at any time during the process.

- Whenever possible, researchers should avoid data collection during regular class meetings. When study participation consumes a significant portion of a class session, loss of instructional time for both participants and non-participants may be considered a loss of benefits. Also when research participation is expected during the same session at which participation is invited students may be unduly influenced to take part due to peer pressure, perceived stigmatization from non-participation, or a sense of having otherwise wasted time by attending that day's class.

- Since there are special risks of confidentiality in the close environment of the university, special attention should be given to full disclosure of these risks in the consenting of a student to participate. The plan for handling consent forms and research data should also be designed to minimize the risk that confidentiality will be breached (e.g., signed consent forms can be collected and filed separately from the anonymous test instrument). When instruments call for the disclosure of information which participants may view as personal or sensitive, data should be collected in a manner that minimizes the chance of one participant learning the response of another. In most instances the IRB will require that the study be designed so that the faculty investigator does not obtain IDENTIFIABLE, sensitive information about student subjects

- The use of mass testing (classroom scenario) is strongly discouraged. Whenever possible, students should be allowed to access web-based research related activities via designated or personal computers.

- Like other research volunteers, students who become research participants must be allowed to withdraw from the study at any time. The informed consent statement should make clear the consequences of withdrawing from a project prior to completion. In general it is favorable to give credit if the subject withdraws, unless the student withdraws immediately or there is evidence of bad faith on the part of the student.

- If the research is one where data are collected from a group project or perhaps a videotape of the group interaction, each student's consent is necessary for the use of that data in the instructor's research. If one student does not consent, the data may be used only if the non-consenting student's data can be effectively excluded.

- When deception is used students have the right to full disclosure as soon as possible. *Two consenting presentations are required*, the first of which will normally take place during the pretesting period; the final informed consent will be presenting at the *debriefing*. Whenever possible a teaching opportunity in the form of an "educational debriefing" should be employed. Students should know something about the rationale for the study, the process of data collection, and intent of the researcher. In exceptional circumstances, the full or true purpose of the research may not be revealed to the subjects until the completion of data collection. In such cases, students must not be subjected to undue stress or embarrassment and must have the right to full disclosure of the purpose of the study as soon as possible after the data have been collected. During the debriefing students must be given an opportunity to decide whether the researcher(s) can use the data collected.

- Research conducted by graduate students in a class in which the researcher teaches, assists in the class or does any grading should be subject to the same restraints described above.

For additional questions regarding the enrollment of BU students as study subjects please contact the IRB office at 617-358-6115 or irb@bu.edu.

These Guidelines are patterned after those developed at the University of Texas at Austin.

