

# Policies and Procedures

---

CHARLES RIVER CAMPUS, INSTITUTIONAL REVIEW BOARD

VERSION DATE: DECEMBER 1, 2023



## Contents

1. Introduction .....	4
1.1 IRB Authority .....	4
1.2 Ethical Principles.....	4
1.3 Applicable Federal Regulations .....	4
1.4 Applicable Commonwealth of Massachusetts Laws.....	5
1.5 IRB Autonomy .....	5
1.6 Institutional Support and Responsibility for the IRB .....	5
1.7 Institutional Official for the IRB .....	6
2. IRB Operations.....	7
2.1 Research Activities Reviewed by the CRC IRB .....	7
2.2 Research Activities for Which the CRC IRB Will not Normally Provide Review.....	7
2.3 Responsibilities of the IRB.....	7
2.4 IRB Composition.....	7
2.5 IRB Chair Requirements .....	8
2.6 IRB Member & Alternate Requirements.....	9
2.7 Use of Consultants.....	10
2.8 IRB Member Confidentiality.....	10
2.9 IRB Member Conflicts of Interest.....	10
2.10 Indemnification .....	11
2.11 Meeting Schedule .....	11
2.12 Quorum Requirements .....	11
2.13 Review System .....	12
2.14 Scientific Review .....	12
2.15 IRB Administration .....	13
2.16 Quality Improvement Program.....	13
2.17 IRB Recordkeeping .....	15
3. Investigator and Research Personnel Requirements.....	19
3.1 Principal Investigators (PIs) .....	19
3.2 Investigators and Research Personnel .....	20
3.3 Investigator Conflicts of Interest.....	21
4. Recruitment and Informed Consent Guidelines .....	22
4.1 Recruitment Guidelines .....	22
4.2 Payments to Research Participants.....	23
4.3 Informed Consent Guidelines.....	24
4.4 Required Elements of Informed Consent [45 CFR 46.116(b) and 21 CFR 50.25]:.....	25
4.5 FDA Informed Consent Requirements.....	26

4.6	Documentation of Informed Consent .....	27
4.7	Approval of Consent Materials .....	27
4.8	Informed Consent by Legally Authorized Representatives.....	27
4.9	Subjects who are Non-English Speaking or have Limited Understanding of English.....	28
4.10	Witness to the Consent Process.....	28
4.11	Waivers and Alterations of Informed Consent.....	28
4.12	Posting of Clinical Trial Consent Forms .....	30
5.0	IRB Review of Research involving Human Subjects .....	31
5.1	IRB Review of Grants and Contracts Supporting Human Subjects Research .....	33
5.2	Scientific Review .....	34
5.3	Approval Criteria.....	34
5.4	Exempt Research.....	35
5.5	Expedited Review of Research.....	38
5.6	Review by the Convened IRB .....	41
5.7	Research Requiring Review More Often than Annually.....	42
5.8	Single IRB Review, Ceded Review and Reliance Agreements .....	43
5.9	Privacy and Confidentiality in Research .....	46
5.10	Certificates of Confidentiality .....	47
5.11	International Research.....	48
5.12	ClinicalTrials.gov .....	50
6	Continuing Review of Research.....	54
6.1	Research Requiring Verification from Sources other than Investigators that no Material Changes have occurred since the last IRB Review .....	55
6.2	Study Closure .....	56
7	Modifications to Approved Research.....	57
8	Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others.....	59
8.1	Reporting Requirements to the IRB .....	60
8.2	IRB Review of Reported Events .....	61
8.3	Data Safety Monitoring Boards/Safety Monitoring Committees and External Events .....	63
8.4	Reporting Requirements to Authorities.....	64
9	Protocol Deviations and Issues of Non-compliance.....	66
10	Suspension or Termination of Research.....	69
11	Populations Vulnerable to Coercion or Undue Influence and Special Protections .....	71
11.1	Research with Pregnant Women .....	71
11.2	Research with Prisoners .....	71
11.3	Research with Children .....	75
11.4	Research with Persons with Impaired Decision-Making Capacity .....	79
11.5	CRC Employees, Students, Post-Doctoral Trainees .....	81
11.6	Investigator Self-Experimentation.....	82
11.7	Persons who are Economically or Educationally Disadvantaged .....	82

11.8 Subjects in Harmful Situations: Abuse, Suicide, and Threat of Harm.....	82
12 FDA Regulated Research .....	84
12.1 Research Involving Investigational Drugs .....	86
12.2 Use of Controlled Substances in Research.....	88
12.3 Use of Devices in Research.....	89
13 Community Engagement and Information for Research Participants and Family Members.....	94
13.1 Community Engagement.....	94
13.2 Research Participant Rights.....	95
13.3 Questions, Complaints or Concerns .....	95
13.4 Research Resources for Prospective, Current Research Participants and Family Members.....	96

## 1. Introduction

Boston University (BU) maintains two Institutional Review Boards (IRBs). One IRB serves the Boston University Medical School and Campus, including the School of Public Health and Boston Medical Center, the other IRB serves the Charles River Campus (CRC) and its colleges and institutes. The two IRBs are separate entities, with separate policies and procedures, FederalWide assurances and accreditations.

The BU CRC Institutional Review Board (IRB) is comprised of CRC faculty and staff, as well as members of the greater Boston community. The CRC IRB provides oversight for the protection, rights and welfare of individuals participating in research conducted at BU or by BU Investigators, in compliance with applicable federal and state regulations, institutional policies, and accepted ethical guidelines.

This Policy and Procedure manual applies to all research involving human participants conducted completely or partially at CRC facilities, conducted in approved off-site locations by CRC researchers, and/or conducted by CRC researchers while on official BU time or business. CRC researchers include but are not limited to students, employees, members of the research staff, post-doctoral trainees, and faculty.

BU CRC holds a FederalWide Assurance (FWA00002457) and an IRB Registration (IRB00008274) with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). It is accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP).

### 1.1 IRB Authority

The CRC IRB has the following authority:

- To approve, require modifications to secure approval, or disapprove all research activities involving human research participants overseen and conducted by the Institution;
- To suspend or terminate approval of research that is not being conducted in accordance with IRB requirements or that is associated with unexpected and/or serious harm to participants;
- To impose any conditions on the conduct of the research that it deems appropriate. This may include observing or having a third party observe the consent process and/or the conduct of the research, as well as other conditions outlined throughout this policy document.

### 1.2 Ethical Principles

The CRC IRB is guided by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research *Ethical Principles & Guidelines for Research Involving Human Subjects*, also known as ‘The Belmont Report’. The basic ethical principles espoused in the Belmont Report include Respect for Persons, Beneficence, and Justice, which are applied in practice in the informed consent process, the assessment of the risks and benefits to the participants, and the equitable selection of participants in the research.

### 1.3 Applicable Federal Regulations

The CRC Human Research Protection Program (HRPP) complies with DHHS regulations at 45CFR46 and its subparts for the protection of human research participants. The regulations at 45CFR46 and its subparts provide the basis for review and approval of all research at the CRC regardless of funding source, and where there is no external funding supporting the research.

When research is regulated by the FDA the regulations at 21 CFR Parts [11](#), [50](#), [54](#), [56](#), [312](#), [314](#), [600](#), [812](#), and [814](#) apply, as applicable, regardless of funding source. These regulations may apply in addition to the requirements of 45CFR46.

The CRC IRB performs the functions that an IRB is required to perform in compliance with [45CFR160](#) and

[164](#), and this policy for the use and disclosure of research participants protected health information.

#### **1.4 Applicable Commonwealth of Massachusetts Laws**

Laws that are specific to Massachusetts and may impact research involving human participants covered by this policy include:

- Individual rights to consent (e.g., 103 CMR 180.07 [prisoners], MGL c. 111 s. 70E [hospital patient's right to refuse participation in research], MGL c. 112 s. 12E [minors with drug dependencies], MGL c. 112 s. 12F [emergency and other treatment of minors and emancipated minors], 104 CMR 31.02 and 31.05 [consent of mental health patients]).
- Confidentiality, such as the Patient Bill of Rights (MGL c. 111 s. 70E); laws that protect various forms of records and information (e.g., MGL c. 111 s. 119 [venereal disease], MGL c. 111 s. 70F [HIV results], MGL c. 111E s. 18 [drug abuse treatment], MGL c. 111B s. 11 [alcohol abuse treatment], MGL c. 111 s. 70G [genetic privacy]); and laws that privilege various clinical relationships (e.g., MGL c. 112 s. 135 [social worker-patient privilege], MGL c. 233 s. 20B [psychotherapist-patient privilege], MGL c. 112 s. 129A [psychologist-patient privilege], MGL c. 233 s. 20K [domestic violence counselors])
- Mandated reporting (e.g., MGL c. 119 s. 51A [child abuse and neglect reporting], MGL c. 111 s. 6 ([infectious disease reporting], MGL c. 19A s. 15 [elder abuse reporting])).
- Genetic testing and release of genetic results (MGL c. [111 s. 70G](#)).
- Research on fetuses (MGL c. 112 s. 12J) and involving human embryonic stem cells (MGL c. 111L).
- Research projects that involve controlled substances and investigational drugs (MGL c. 94C s. 8).
- Guardianships (persons who are mentally ill [MGL c. 201 s. 6]) (persons with mental retardation [MGL c. 201 s. 6A]) (persons unable to communicate informed decisions (MGL c. 201 s. 6B)).
- Health Care Proxies [MGL c. 201D].
- Research under the jurisdiction of the Department of Mental Health (104 C.M.R. § [31.00](#) and 104 CMR § [31.01](#)), and the Department of Developmental Services ([115 CMR 2](#) and [115 CMR 10](#)).

The CRC IRB consults with its representative from the Office of General Counsel in areas where federal and state regulations are not cohesive, when new or revised regulations or guidance are issued and require further interpretation, or when the application of federal or state laws is unclear given the facts of a specific circumstance.

#### **1.5 IRB Autonomy**

No individual or group of individuals may try to influence the deliberations and decisions of the IRB. IRB members may report any attempt to influence their decisions to the IRB Director (ID), the Executive Director of Research Compliance (EDRC), the Institutional Official (IO), or a representative from the Office of General Counsel (OGC), and they will investigate any such reports.

#### **1.6 Institutional Support and Responsibility for the IRB**

To ensure an autonomous IRB and compliant research program, CRC Administration is responsible for:

- Establishing and supporting a culture of compliance with federal regulations, institutional policies, and ethical principles for the protection of human research participants;
- Appointing an IO legally authorized to act for the CRC to oversee the HRPP at the CRC and ensure its effective function in compliance with the terms of the CRC's FWA and applicable regulations;
- Appointing an IRB Director to oversee the operations of the IRB;
- Providing adequate resources to the IO to support the activities of the IRB and IRB staff;
- Publicizing IRB policies, procedures and forms;
- Assuring that BU CRC personnel with competing business interests, such as those responsible for business development and raising funds, cannot be responsible for day to day operations of the IRB review process.

CRC officials may not approve research involving human research subjects that has not been approved by the CRC IRB. However, CRC officials may disapprove research, independent of the IRB, and even where the research is otherwise approvable and/or approved by the IRB.

### **1.7 Institutional Official for the IRB**

The Associate Vice President Research Compliance (ACPRC) serves as the CRC IRB's Institutional Official (IO). The IO reports to the Vice President and Associate Provost for Research. The budgets for the IRB, as well as those for Research Compliance, are under the IO's supervision. The Institutional Official represents the BU CRC on the Federalwide Assurance (FWA) and serves as the Signatory Official. The Institutional Official is ultimately responsible for ensuring that the Boston University Charles River Campus is in compliance with federal requirements. The IO is responsible for:

- Appointing a qualified IRB Chair and IRB members in accordance with OHRP guidance, and periodically reviewing the membership of the IRB to ensure appropriate expertise and experience to the type of research ordinarily reviewed;
- Performing periodic evaluation of the performance of the IRB Chair and IRB members;
- Suspending or terminating the IRB membership or Chair appointment of anyone who is not fulfilling his or her responsibilities and obligations;
- Assuring individuals with competing business interests, such as those responsible for business development and raising funds for BU, cannot serve as members of the IRB;
- Selecting an IRB staff who demonstrate appropriate knowledge and experience for their roles and performing periodic evaluation of their performance;
- Providing educational opportunities for IRB members, IRB staff, Investigators, Research staff, and BU leadership where appropriate;
- Assuring independent actions of the IRB, including freedom from undue influence or coercion by officials or others at the Institution;
- Ensuring IRB access to legal counsel with expertise in human subject protection issues;
- Providing adequate resources, including office and meeting space, office supplies, and staffing to support the IRB's operations and responsibilities;
- Reviewing and signing agreements between the institution and other organizations, including those that establish reliance on IRBs of record for collaborative research;
- Providing guidance with complex issues, such as conflicts of interest, or serious or continuing non-compliance;
- Communicating with federal oversight agencies (e.g. OHRP, NIH, FDA) when necessary.
- Ensuring that CRC Investigators comply with IRB policies, the terms of the CRC's FWA and applicable Federal regulations that govern the protection of human research participants.
- Suspending or terminating research as needed and on an urgent basis in between IRB meetings, and reviewing appeals, as appropriate, by investigators of suspensions and terminations;
- Setting the "tone" for an institutional culture of respect for human subjects;
- Ensuring that investigators fulfill their responsibilities for the ethical conduct of human subjects research;
- Serving as a point of contact for OHRP and other regulatory agencies;
- Communicating with and advising other senior management officials on human subjects protections issues as necessary.

## **2. IRB Operations**

### **2.1 Research Activities Reviewed by the CRC IRB**

A variety of human research activities are conducted at the CRC and by CRC Investigators, including:

- Social, behavioral, and educational research;
- Biomedical research;
- FDA-regulated research, including research involving drugs that require an IND and devices that require an IDE.

### **2.2 Research Activities for Which the CRC IRB Will not Normally Provide Review**

Based on the typical population the CRC serves and the nature of the research conducted at the CRC and by its Investigators, and given the baseline composition expectations for the CRC IRB, the following categories of research will not normally be reviewed by its IRB absent special circumstances and preparation:

1. Research involving a waiver of consent for planned emergency research;
2. Activities (both research and treatment protocols) involving humanitarian use devices;
3. Research using Broad Consent under 45CFR46.116(d);
4. Research using limited IRB Review under 45CFR46.104(d)(7 and 8)

While the CRC IRB does not ordinarily review the above-noted research, with advanced-notice by an Investigator the IRB Director may be able to arrange to review or cede review of a specific protocol or category of research in items 1-4 (above) to another institution with an IRB that is appropriately constituted to review such research activities.

### **2.3 Responsibilities of the IRB**

The responsibilities of the IRB include reviewing and overseeing research activities conducted by BU CRC Investigators in a manner that is compliant with applicable federal and state regulations, institutional policies, and ethical guidelines for the protection of human subjects. The IRB should ascertain the acceptability of proposed research in relation to institutional commitments, applicable laws and standards of professional conduct and practice. This includes the following activities, which are outlined in more detail throughout this policy document:

- Determining whether a proposed activity meets the definition of ‘Research’ or research involving ‘Human Subjects’;
- Determining whether any proposed Human Subjects Research is exempt from IRB review and oversight and informed consent pursuant to 45 CFR 46 and [21 CFR 56](#);
- Except when an expedited review procedure is used in accordance with regulatory requirements, reviewing proposed research at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas;
- Conducting reviews of initial and continuing research, proposed changes to approved research, unanticipated problems involving risks to research participants or others, and allegations of serious or continuing noncompliance with applicable regulations, policies or the requirements of the IRB;
- Reporting IRB findings and actions to the Investigator, and to the Institution, granting agencies and federal and state authorities when appropriate;
- Determining which projects require review more often than annually and which projects need verification from sources other than the Investigators that no material changes have occurred since the last review.

### **2.4 IRB Composition**

Per regulations at 45 CFR 46.107, the CRC IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the Institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional



competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of participants.

Additionally:

- The IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
- No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
- An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.
- Individuals who are responsible for business development are prohibited from serving as members or ex-officio members on the IRB and from carrying out day-to-day operations of the review process.

## 2.5 IRB Chair Requirements

**Appointment:** The IO, EDRC and IRB Director are responsible for selecting the IRB Chair and Vice-Chair. The selection process is conducted in consultation with respective School Deans, Department Chairs, and other IRB members.

The IO will appoint the IRB Chair and Vice-Chair by way of an appointment letter; there is no time limit for serving as an IRB Chair or Vice-Chair. The IRB Chair or Vice-Chair may resign at any time by submitting a letter of resignation to the IO, EDRC or IRB Director. The IO may remove the IRB Chair or Vice-Chair from the committee if they are not able to fulfill their responsibilities.

**Qualifications and Training:** The Chair should be proficient in research, and without conflicts of interest that would curtail his or her ability to serve objectively and according to the mission of the IRB. The Chair will have successfully completed the [CITI training](#) for the protection of human subjects in research and will attend other trainings (such as those offered by [PRIM&R](#) or internally at BU) as requested or required by the IO, but not less than once every three years.

**Responsibilities:**

- Ensuring compliance of IRB actions with federal and state laws, institutional policies, ethical guidelines, and the terms of the CRC's FWA, where applicable;
- Presiding over the majority of convened IRB meetings, allowing sufficient time and opportunity for members present to discuss and vote on the studies under review, and to provide clarification and leadership for members;
- Identifying when additional expertise beyond that represented by the IRB membership would be necessary or useful in the review of a particular protocol;
- When necessary, communicating with the IO, IRB Staff, IRB members and/or Principal Investigators when there are issues with the review of research, or the design and/or conduct of research;
- Constituting sub-committees of the IRB as appropriate to address specific issues, including the

- Participating in the development and approval of IRB policies and procedures, and other materials to be used as resources for Investigators and IRB members;
- Serving as an IRB member;
- Reviewing minor deviations and/or other events that qualify for review by expedited procedures;
- Assisting with investigations/audits of investigators;
- Reviewing and signing correspondence related to IRB determinations;
- Ensuring that IRB members with a conflict of interest are not present for the discussion and vote on the research where they have a conflict;
- Conducting review of IRB minutes;
- Assisting with the selection of new IRB members;
- Assisting with the annual evaluation of the IRB and IRB members.

**Responsibilities of the Vice-Chair:**

- Serving as an IRB member;
- Supporting the IRB Chair;
- Assuming the duties of the IRB Chair when the Chair is not available or has conflict of interest in a study under review.

**Evaluation:** An evaluation of performance of Chair and Vice Chair duties and responsibilities will ordinarily be conducted each year by the IRB Director, EDRC, and IO.

## 2.6 IRB Member & Alternate Requirements

**Appointment:** IRB members are selected by the IO upon the recommendation of the IRB Director. IRB members are asked to serve for a minimum of three years; however, there is no term limitation. The IRB is comprised of members with experience in the scientific disciplines of research typically conducted at BU, as well as the larger community served by the CRC.

**Training:** CRC IRB members will have successfully completed the [CITI training](#) for the protection of human subjects in research and will attend other trainings as requested or required by the IO, EDRC, or IRB Director. Each new IRB member has access to the CRC IRB Policies and Procedures, relevant DHHS and FDA regulations, commonly referenced OHRP guidance, as well as a copy of the Belmont Report. In addition to these materials, any updated regulations, education and policy materials will be circulated with the monthly meeting packets and reviewed at convened IRB meetings.

**Alternate Members:** Alternate members are appointed to serve as a substitute for primary IRB members and to ensure that the IRB has the appropriate quorum and/or expertise to review research (e.g. prisoner representative, pharmacy representative, etc.). The IRB roster ordinarily will indicate which member or category of member (e.g. non-scientist) for which the alternate may substitute. When an alternate member substitutes for a primary IRB member, the alternate receives and reviews the same materials as the primary members. The IRB minutes will document when alternate members substitute for a primary member. If a primary member and their alternate attend the same IRB meeting, the primary member is acting as the official voting member, unless the minutes clearly indicate otherwise. An alternate may substitute for an entire meeting or at any time during a meeting (e.g. review of a specific protocol).

**Responsibilities of IRB Members (primary and alternates):**

- Attending monthly IRB meetings and participating in the review of research;
- Completing human subjects research training;
- Conducting and/or assisting with review of research by expedited procedures;
- Serving on IRB sub-committees as needed;
- Working with investigators to resolve issues related to IRB review;
- Maintaining current knowledge of applicable regulations, laws, and institutional policies;

- Participating in discussions of issues related to the review of human subjects research, including policy development;
- IRB members should report any attempts of undue influence to the IO.

**Evaluation:**

**Composition of the IRB:** The composition of the IRB will be reviewed on an annual basis to ensure that it meets institutional and regulatory requirements. This review will be conducted by the IRB Chair, IRB Director, and EDRC, in consultation with the IO.

**IRB Members:** IRB members are ordinarily evaluated on an annual basis on their attendance, performance and participation in convened meetings (including subcommittee meetings), and as primary and secondary reviewers. This review will be conducted by the IRB Chair, IRB Director, and EDRC, in consultation with the IO.

**2.7 Use of Consultants**

If the board does not have the appropriate expertise to review a research study, a consultant may be used to assist in the IRB review. Consultants may be used for exempt, expedited, and full board studies. The IRB Director and/or Chair will determine if a consultant is needed. In addition, any member of the IRB may request the use of a consultant during the review process. The consultant will be asked to provide a written review. If recommended, the consultant may be asked to attend the meeting. Consultants may be used to provide specific content information to the IRB, but these individuals are not IRB members and therefore not permitted to vote. The use of consultants will be documented in the meeting minutes.

**2.8 IRB Member Confidentiality**

The IRB, at times, reviews sensitive and private information. IRB Members (and any invited guests, including consultants) are expected to keep all materials and discussions pertaining to IRB business confidential. The Chair will make efforts at the start of convened meetings to remind members of their confidentiality obligations.

**2.9 IRB Member Conflicts of Interest**

All IRB members with a possible conflict of interest (COI) must identify the conflict prior to review of the impacted research and recuse themselves from the review, if appropriate. A COI is considered to exist where an IRB member’s own professional, personal or financial interests (as further explained below) may reasonably be found to directly and significantly impact the member’s review of the research, whether positively or negatively. No IRB member with a COI will be allowed to provide a review, a determination, or a vote on research with which they have an actual or perceived conflict. This policy is applicable to consultants who may be engaged to review research activities, and IRB staff who serve as IRB members.

**COI Disclosure at Convened IRB Meetings:** The Chair calls for COI disclosures upon confirming quorum. The Chair additionally requires disclosure from any member who arrives after quorum has been confirmed if that person was not present for the initial disclosure. IRB members with identified conflicts and who have additional information about the research may provide that information to the IRB if so requested, but that member may not be present for the discussion or the vote.

**COI Disclosure during Expedited, Exempt, Not Research, and Not Human Subjects Review Procedures:** COI disclosure is required on the Reviewer Sheets at the time of review. If a COI is disclosed, the IRB Staff will identify another IRB member, without a COI, to review the research.

**Conflict of Interest:** Any situation in which an IRB member has an interest (financial or non-financial) in the research being reviewed, in example:

- **Professional:** has a role in the study (such as a co-Investigator or collaborator); supervisory/mentoring role over someone on the research team; is supervised/mentored by someone on the research team; is a member of a board supporting the study; or may suffer a professional loss, such as standing in the professional community if the study is or is not approved. IRB members who are colleagues in the same department of an Investigator whose research is under review are not necessarily considered to have a professional conflict of interest. Such members should use their discretion on whether they may feel bias or pressure to approve or disapprove the research and should contact the IRB Chair and/or IRB Director with any questions.
- **Financial:** the IRB member or his or her family member (defined here as a spouse, domestic partner, and dependent children) has any financial interest in the study under review, including the potential for financial gains or losses through payments or consulting fees, equity interest or intellectual property rights from the research study or its sponsor or in the design, conduct, or reporting of the research; has received payments from the Sponsor in any amount; is an executive director, board member, scientific advisor, or holds other decision-making positions of the agency or company sponsoring the research. While it is possible for financial conflicts held by Investigators to be managed under the BU Conflicts of Interest Policy, IRB members must recuse themselves from reviewing any study in which they have any financial conflict, as defined above.
- **Personal:** is the spouse, dependent, domestic partner or relative of an Investigator on the study under review or has some other type of personal history with an Investigator that would bias or would be perceived as biasing the IRB member's review of the research.

Any other reason for which the IRB or IRB member believes they have a conflict of interest with the research.

**Consultant Conflict of Interest:** Consultants will follow the same policy for identifying, disclosing, and managing conflicts of interest as IRB members. If a consultant has a conflict of interest, they will not be assigned to the project; however, if they are the only appropriate resource for the IRB (e.g. is the only person with sufficient understanding/expertise of the project) they will be allowed to provide the requested information to the IRB, provided that the conflict is also disclosed to the IRB (or IRB member, in the event of expedited review, exemption and other determinations) ahead of the review and vote.

## 2.10 Indemnification

The CRC IRB, as well as its individual members, is/are indemnified under the BU professional and general liability insurance policies up to certain financial limits, provided that the IRB and its members are acting within the scope of their role on the IRB, and in good faith.

## 2.11 Meeting Schedule

The CRC IRB ordinarily meets on the third Tuesday of every month. On occasion, meetings are held on different days and times, depending on holiday or quorum issues, or extenuating circumstances. "Emergency" meetings are not ordinarily called unless safety issues or significant regulatory issues have been identified with a study or Investigator. Subcommittee meetings are held on an ad hoc basis, depending on necessity. When there are no protocols to review or business to conduct, meetings may be cancelled.

## 2.12 Quorum Requirements

Quorum requirements are the majority of the IRB, inclusive of at least one non-scientific member (i.e. if the membership is 8, then the quorum is 5, and if the membership is 9, then the quorum is 5). IRB members are encouraged to attend all convened meetings (for reasons such as last-minute quorum issues, scientific expertise, experience with previous reviews of a study, and familiarity of studies conducted by an Investigator). If quorum is not attained or is lost during the meeting, no actions may be taken by the IRB until

the quorum exists or is restored. IRB staff are responsible for ensuring quorum for the convened meetings, and during the meetings. Approval of research requires a vote to ‘approve’ by a majority of IRB members present (in person, by phone, or videoconference) at a convened meeting.

### 2.13 Review System

IRB Reviewers are selected from the IRB members by the IRB Director and/or Chair or their designee. Whenever possible, Reviewers will have expertise appropriate to the review of the assigned study. If this is not possible, or if the Reviewer does not believe that they have the appropriate expertise, the IRB Director will arrange for another member to review the protocol, seek a consult, or defer the review until appropriate expertise has been secured.

Reviewers are responsible for conducting a thorough evaluation of all protocol materials submitted by the Investigator, and any additional materials for reference provided by the IRB staff. In general, protocol review materials should provide sufficient detail to permit the IRB to make an informed judgment about whether to approve a study. Where the submission requires more information, the Reviewer may either ask the IRB staff to request this information from the Investigator or contact the Investigator directly.

- **Convened IRB Review:** Research that does not meet exemption or expedited review criteria is reviewed by the convened IRB. A primary reviewer system is used for studies under review by the convened IRB. Ordinarily, a primary (and a secondary reviewer, if needed), are assigned to each research protocol on the convened meeting agenda, including for initial and continuing reviews, amendments, incidents, etc. The Reviewer is responsible for presenting the research proposal at the convened meeting, including raising any issues or questions, and their recommendation for approval. The secondary reviewer is chosen to present the study if the primary reviewer is unable to attend the meeting, or if the issues presented in the study are unusually complex. The secondary reviewer may have additional expertise relevant to the study or may be a new IRB member added as a Reviewer to gain experience. The IRB Chair ordinarily serves as the Reviewer for reported unanticipated problems involving risks to participants or others, and allegations of serious or continuing non-compliance.
- **Expedited Review:** The IRB Chair designates experienced IRB members to review research that meets expedited review criteria at [45 CFR 46.110](#). IRB members, including those who are IRB analysts, make these determinations. An experienced member is one who has at least six months of IRB experience, has received training relative to the expedited review categories, and has the appropriate background and knowledge to conduct the review. If the research involves prisoners, the IRB Prisoner Representative must serve as one of the reviewers.
- **Exempt Review:** The CRC IRB is responsible for determining if a research activity is exempt from the regulations at [45 CFR 46.104](#). IRB Analysts who are IRB Members determine if the research qualifies as exempt and serves as a reviewer for the exempt protocols. IRB Members with specific content expertise may be asked to serve as reviewers along with the IRB Analyst for certain research studies.

### 2.14 Scientific Review

The scientific and scholarly review is conducted in the following ways, as applicable:

- The peer review process for federally sponsored research (e.g. NIH, DoD, etc.);
- Independent peer review process for other sponsored or foundation research;
- FDA review of research regulated under their guidelines (e.g. IND or IDE Application review);
- The Faculty Advisor for all research where a student is PI;
- The Department Chair and/or Dean is required to sign-off on all new IRB Applications;
- During IRB review, the Primary Reviewer ordinarily has the appropriate expertise;
- If vulnerable populations are involved, ordinarily an IRB member with the appropriate expertise will

review the study;

- If the IRB does not have the appropriate expertise for a review, it will request a consultant with the needed expertise (internal or external to BU);
- The PI will provide additional information and/or present to the IRB, as needed.

During review, the IRB will determine whether:

- The study is designed to minimize the risks to subjects;
- The potential risks to subjects are justified by the potential benefits of the research;
- The study utilizes procedures which are consistent with sound research design;
- Study procedures do not unnecessarily expose subjects to risks;
- The knowledge to be gained from the research has significance or importance;
- The Investigator-completed IRB Application accurately describes the research objectives, background, location, procedures, data and safety monitoring, and the risks and benefits for participants;
- The investigators have the appropriate experience and training, resources and facilities to conduct the study.

## **2.15 IRB Administration**

The IRB is supported by professional staff who manage the day-to-day administration and operation of IRB activities. The responsibilities of the IRB staff include:

- Developing policies and procedures, IRB Applications and other support materials in accordance with federal regulations, state/local laws, ethical guidelines and institutional policies;
- Conducting a pre-review of all submitted materials, communicating with Investigators regarding any submission deficiencies, and preparing the submission materials for review by expedited procedures or by the convened IRB;
- Documenting the proceedings of IRB meetings and the determinations resulting from IRB review;
- Communicating IRB determinations to Investigators;
- Providing advanced notification to Investigators when materials are due for continuing or annual review;
- Maintaining records of IRB activities;
- Facilitating effective communication among the IRB members, Investigators, staff, department heads, administrators, and institutional officials;
- Maintaining the Institution's FederalWide Assurance (FWA) and IRB Registration with OHRP, and promoting compliance with the terms of the FWA;
- Providing education and training opportunities to IRB members, BU staff and Investigators.
- Communicating with federal oversight agencies (e.g. OHRP, NIH, FDA, etc.) when necessary, and in consultation with the EDRC and/or IO.

All IRB staff must complete training in human research protection through CITI upon employment, and certification must not be more than three years old. IRB staff who are responsible for IRB Operations (e.g. development of policies, procedures, review processes, etc.) and who are Senior Analysts should ideally hold a Certified IRB Professionals (CIP) upon hire or within two years of hire or as agreed upon with the IRB Director, and recertification shall be ongoing. IRB Staff may attend local and national conferences and workshops on human subject protection issues.

## **2.16 Quality Improvement Program**

The CRC Human Research Protection (HRP) Quality Improvement (QI) program promotes the ethical conduct of research, compliance with applicable regulations and institutional policies, evaluates and monitors the effectiveness and efficiency of the IRB, and assists with the development and implementation of best practices in human subjects research. The QI program evaluates and improves HRP activities on an ongoing basis through education, training, and monitoring of the CRC Human Research Protection Program, including the IRB, Investigators and their research.

The QI Program conducts for-cause (e.g., due to compliance issues, complaints, concerns, etc.) and not-for-cause reviews (e.g., random selection, PI request, new clinical trial start-up, etc.).

- **For-cause reviews:** For-cause reviews are ordinarily initiated by the IRB or other university officials as a result of noncompliance, complaints (e.g. subjects, research staff, etc.), concerns, or to obtain or verify information. Documentation typically reviewed during these visits include regulatory materials (IND/IDE letters, clinicaltrials.gov registration, regulatory criteria, etc.), IRB documentation (approval letters, approved protocols, consent forms, etc.) and study documentation (data collection materials, signed consent forms, etc.).

For-cause reviews typically occur at the research site and include a meeting at the beginning of the visit to discuss any specific concerns, the QI visit process, and to obtain feedback from the investigators and/or research staff. If non-compliance or unanticipated problems are discovered during the review, it is the responsibility of the PI to report these events to the appropriate office (e.g., IRB, COI, SP or Study Sponsor, etc.). If the PI does not report the events in a timely manner, the QI representative will report the event to the appropriate committees/individuals. The QI representative will complete a report of the review. The report will be shared with the IRB Director and/or other institutional/university officials. The PI will be given the opportunity to review the report prior to it being sent to the IRB and/or other institutional/university officials.

- **Not-for-cause reviews:** Not-for-cause reviews are ordinarily initiated by the QI program, the result of IRB request/requirement, or a request from the PI.
  - QI-Initiated reviews are conducted on a rolling basis. Research selected for these random reviews are based on criteria such as research that poses potential compliance issues (e.g., complicated study designs), research involving vulnerable populations, Investigators/departments with a high volume of international research, student researchers who serve as PIs, and research that poses greater than minimal risk to study participants.
  - New-PI Study Start-up is a voluntary service offered by the QI Program to assist new PIs and their research staff with preparing for their responsibilities in conducting research. The QI program will provide the necessary tools and information to enhance compliance with the regulations, IRB policies and procedures. These visits may occur prior to enrollment or during the early stages of the study. The QI representative may determine that a study start up visit is not appropriate for a given investigator and may instead conduct a review of the IRB file and email the investigator with any relevant compliance-related information. Participation is voluntary.
  - PIs of any level of experience may request a QI review for quality assurance and/or improvement purposes, or to help prepare for an external (e.g., sponsor, FDA, etc.) or internal (e.g., risk management, financial services, etc.) audit.
- The IRB may request or require QI reviews, for-cause and not for-cause, including:
  - Per CRC IRB requirement, all FDA-regulated studies will undergo QI review after obtaining IRB approval. The IRB may determine the timing of this review or may leave the timing up to the QI program in consultation with the PI.
  - In accordance with 45 CFR 46.109(g) and 21 CFR 56.109(f), the IRB has the authority to observe, or have a third party observe the consent process and the research. The IRB may require observation of the consent process in a research study in circumstances such as: a reported problem with the consent process by a participant or study team member, an investigator with significant or ongoing compliance issues, enrollment of vulnerable populations, and other situations in which the IRB and/or institutional/university officials feel that observation is necessary in order to ensure compliance and to protect the rights, safety, and welfare of the subjects.

## QI Review of HRPP Activities

In addition to the review of research and researcher activities, the following Quality Improvement activities of the HRPP occur:

- **HRPP Resources:** On an annual basis, the IRB Director, Executive Director Research Compliance, and the Institutional Official will evaluate the resources needed for the HRPP. This may include but is not limited to office space and material resources, IRB personnel, commitments made to accrediting agency, HRPP education program activities, access to legal counsel, conflict of interest assessments, quality improvement plans, community outreach, IRB composition and number of Boards to meet the needs of the CRC research community.
- **IRB Metrics:** Metrics are collected and utilized to accomplish goals and objectives set by the IRB and HRPP, ensure compliance with regulations, policies and procedures, improve program efficiency by identifying gaps and bottlenecks, allocating resources to programmatic needs, and assisting investigators in understanding the IRB process. The metrics are ordinarily calculated using calendar days (weekends, holidays, and closures are included) and posted on the IRB website each month. Additionally, metrics are ordinarily provided to the IRB at each convened meeting, and reviewed regularly by the IRB Director, Executive Director Research Compliance and the Institutional Official.
- **Quarterly metrics:** The following metrics are reviewed on a quarterly basis: volume received, volume approved, turnaround time (date submitted to date of approval), PI turnaround time vs. IRB turnaround time, breakdown by IRB Analyst.
- **Website Analytics:** The website analytics are reviewed periodically to determine web traffic, reader interest, and improve the website content and layout.
- **Review/assessment of the IRB:** The QI program will assist the IRB Director and IRB Chair in assessing the IRB to ensure that it is compliant with applicable laws, regulations, and institutional policies. In addition, the QI program will assist in assessing IRB operations to develop and implement best practices for the IRB to be most effective and efficient. These reviews may include but are not limited to: meeting minutes, protocol files, consent forms, IRB determination letters, reviewer checklists and worksheets, exempt and expedited category determinations, consent waivers.
- **Process Review:** Process reviews of the IRB are conducted periodically to evaluate and monitor effectiveness and to improve processes as needed. These reviews may include but are not limited to: metrics, review of feedback from investigators/research staff, review of feedback from research subjects, protocol file review.

### 2.17 IRB Recordkeeping

The IRB recordkeeping complies with the requirements of 45 CFR § 46.115, to prepare and maintain adequate documentation of IRB activities, including the following:

- (1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by Investigators, and reports of injuries to subjects.
- (2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
- (3) Records of continuing review activities, including after January 18, 2019, the rationale for conducting continuing review of research that otherwise would not require continuing review under the Revised Common Rule at 45 CFR 46.109(f)(1).



- (4) Copies of all correspondence between the IRB and the Investigators.
- (5) A list of IRB members in the same detail as described in 45 CFR 46.108(a)(2).
- (6) Written procedures for the IRB in the same detail as described in 45 CFR 46.108(a)(3) and (4).
- (7) Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5).
- (8) The rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in § .110(a) is more than minimal risk.
- (9) Documentation in the form of this policy and procedure manual specifying the responsibilities that CRC IRB will undertake to ensure compliance with the requirements of this policy under § .103(e).

**IRB Review Materials:** The CRC IRB is responsible for maintaining records of IRB actions related to the review and approval of research. The records must allow for a reconstruction of the complete history of IRB actions. This applies to all reviews including initial reviews, continuing reviews, amendments, deviations, unanticipated problems, and other events. IRB records include the following information/documents, as applicable:

- Protocols/IRB Application or research plans
- Data collection materials, surveys, questionnaires, interview scripts, etc.
- Investigator brochure or device manual, if any
- Scientific evaluations when provided by an entity other than the IRB
- BU Ancillary reviews (e.g. IBC, Export, Laser Safety, EHS, etc.)
- Recruitment, informed consent and eligibility screening materials
- Sponsor Progress Reports
- Reports of injuries to participants
- Records of continuing review activities
- Data and safety monitoring report
- Modifications to previously approved research
- Unanticipated problems involving risks to participants or others
- Documentation of non-compliance
- Significant new findings
- All correspondence between the IRB and researchers
- The rationale for conducting continuing review of research that does otherwise would not require continuing review
- The rationale for a determination that research appearing on the expedited review list published in the Federal Register is more than minimal risk
- Rationale for use of expedited review and exemption categories
- Criteria for waivers of informed consent and HIPAA
- Criteria for approval for research with prisoners, pregnant women and children

**IRB Minutes:** Minutes of convened CRC IRB meetings document the following:

- Actions taken by the IRB
- Separate deliberations for each action
- Committee member vote (for, against, abstain) numbers for each protocol documenting quorum
- Committee member and guest attendance at the meeting
- When an alternate member replaces a primary member
- The basis for requiring changes in research
- The basis for disapproving research
- A written summary of the discussion of controverted issues and their resolution
- For initial and continuing review, the approval period
- The names of IRB members who leave the meeting due to a conflict of interest and the reason for the absence
- Rationale for significant/non-significant risk device determinations
- Requirement for IND

- Determinations and protocol-specific findings justifying those determinations
- Waiver or alteration of the consent process and/or documentation of consent
- Extra protections and approval criteria met for research involving pregnant women, prisoners, children and other vulnerable populations.

**Single IRB Review:** When the CRC IRB will either cede IRB review (and therefore be the relying IRB) to another institution or agree to be the reviewing IRB for another institution, there will be a written Agreement that documents the compliance responsibilities of both the relying IRB and the reviewing IRB. This Agreement will be maintained in the IRB file. The file will include the following information, as applicable:

- Process for how information collected will be made accessible to the reviewing IRB
- Process for research site to send information to the overall study PI
- Process for adding additional study sites
- Process for sharing adverse event or other study issues between sites
- Process for notifying sites of modifications to the protocol and study materials
- Process for reporting unanticipated problems and continuing and/or serious noncompliance to the overall PI and reviewing IRB.

**IRB Membership Rosters:** IRB membership rosters contain the members' name, professional degrees, affiliation or non-affiliation with BU, scientific or non-scientific status, any scientific or field specialty, email address, designation as a primary or alternate member and human subject protection training dates. Rosters are modified as changes are made, and final versions are maintained on the IRB shared drive. All changes in membership are made by the IRB Director in consultation with the Executive Director Research Compliance and approved by the IO.

**IRB Policies and Procedures:** The IRB Director is responsible for drafting new policies and procedures and updating existing policies and procedures for compliance with applicable regulations, laws, institutional policies and best practices.

- **Policy and Procedure Approval:** Policies and procedures are presented to the IRB ordinarily at convened meetings for review and approval, though review and approval may also occur via email. The IRB Director or designee is responsible for making any changes required by the Board in order to approve the policy/procedure. After approval by the Board, policies/procedures are sent by the Director to the Institutional Official (IO) for final review and approval. Once approved by the IO, policies will be posted on the IRB website, along with the date of approval.
- **Policy and Procedure Distribution:** New policies and procedures are posted on the IRB website and stored on the IRB shared drive. If the IRB, IRB Director or IO determines that a new or revised policy represents a major change that Investigators need to be aware of, the IRB office may distribute the policy via email to the IRB listserv and other University listservs, as appropriate.
- **Policy and Procedure Revision:** The IRB Director is responsible for revisions to policies and procedures, which are reviewed, approved and distributed in the same manner as new policies and procedures. Minor, non-substantive and/or administrative revisions may be approved by the Director and do not need to follow the process for approving new policies. Once a policy has been revised, the former version of the policy will be archived and saved on the IRB shared drive.
- **Policy and Procedure Review:** The IRB Director is responsible for reviewing IRB policies and procedures on a triennial basis to ensure that they are still in compliance with applicable regulations, institutional policies, and best practices. Revisions will be made as necessary.
- **Internal workflow policies and procedures:** Policies and procedures for internal workflow are drafted by the IRB Director or designee and then reviewed with the IRB staff and stored on the IRB shared drive. The Director gives the final approval of these policies and procedures, which are not reviewed or approved by the IRB or IO. Internal workflow policies and procedures are reviewed and updated as necessary.

**IRB Record Retention:** IRB records are retained for at least seven years after completion and closure of the protocol. If a protocol is closed without participant enrollment, IRB records are maintained for at least seven years after cancellation. Additional information may be found in the [Boston University Record Retention policy](#). Records are accessible for inspection and copying by authorized representatives of federal agencies or departments at reasonable times and in a reasonable manner.

### 3 Investigator and Research Personnel Requirements

#### 3.1 Principal Investigators (PIs)

PIs who conduct human subjects research on the CRC are responsible for ensuring the ethical conduct of human subjects research, protecting the rights and welfare of human subjects, and complying with appropriate regulations, laws, and institutional policies. A PI has full responsibility for the oversight of their research study, including the design, conduct and reporting of the research. The PI is fully responsible for the academic quality of the research and for ensuring compliance with the terms, conditions, and policies of the sponsor and the university. Only one PI may be designated on an IRB application. Those who may serve as a PI on the CRC include:

- BU Faculty per PI policy
- BU Personnel per PI policy
- Students, including undergraduates, graduate and doctoral (note: all students must designate a Faculty Advisor on their IRB application and obtain appropriate approval from their designated school reviewer, as applicable.)

#### PI Responsibilities

- Design and implement ethical research, consistent with the principles outlined in the [Belmont Report](#)
- Ensure that all research involving human subjects approved by the IRB prior to implementation;
- Ensure that anyone delegated to conduct study-related tasks is appropriately qualified and trained;
- Ensure that there are adequate resources to conduct the research;
- Ensure adequate supervision of study personnel;
- Ensure that informed consent is obtained from study subjects in accordance with the IRB approval, and prior to initiating study activities;
- Address concerns/questions raised by research subjects;
- Implement research as it has been approved by the IRB and obtain approval from the IRB prior to implanting any changes to the research;
- Report progress of the approved protocol as required by the IRB;
- Report any new risks, adverse events, unanticipated problems etc., as outlined in the IRB policies;
- Disclose financial conflicts of interest;
- Ensure that a final report is submitted to the IRB when the study is closed or completed.

**PI Qualifications:** Individuals must have the appropriate education, training and experience to serve as the PI of a human subjects research study. The IRB may require additional information from the PI (e.g. CV or Biosketch) or request that the PI add personnel with the appropriate expertise to conduct the study.

**Delegation of Research Responsibilities:** PIs may delegate study-related tasks to appropriately qualified and trained study staff. PIs are responsible for maintaining oversight of their study staff. The PI should develop a plan for supervision to include the following, as applicable: routine meetings to review trial progress, documentation, study events, changes to the protocol, progress and any issues with obtaining and documenting informed consent, addressing any issues identified by study personnel, sponsors, the IRB or outside auditors.

**Faculty Advisor Responsibilities:** If a student is to serve as the PI, the student's Faculty Advisor must sign the IRB Application and certify that they have reviewed the application, agree to serve as the co-investigator for the study, and that they will be responsible for the ethical conduct of the research.

**Principal Investigator Leave of Absence, Sabbatical, Move to Another Institution, or Retirement:** Principal Investigators (PIs) are responsible for timely closure of studies or transfer of responsibilities in the event of an absence for medical or family leave, sabbatical, move to another institution, or retirement.

- In the event of a temporary absence (e.g. parental or medical leave) where a complete return to duties is

expected, a co-Investigator may assume interim PI responsibilities without a formal change of PI.

- In the event of a leave of absence for 3 months or longer, a qualified on-site PI must be formally appointed (note: this is also an NIH mandate), which requires IRB review and approval. The new PI must be willing to assume all PI responsibilities. Any changes to PIs must meet Sponsor requirements.
- When an PI leaves BU (e.g. to move to another institution, or retirement) their original research records must be retained at BU unless approval is received from Research Support.
- The transfer of responsibilities (including those of the PI and the IRB review) should be completed before the PI leaves BU.

### **3.2 Investigators and Research Personnel**

Investigators, including research staff and others who are responsible for the design, conduct, or reporting of the research, have direct interactions with subjects for research purposes (including obtaining informed consent), collect/receive/obtain identifiable research data/specimens, and those who have access to keys/codes with research subject identifiers are required to take applicable training, as identified below. Typically, individuals the PI has assigned study-specific roles and responsibilities (such as co- Investigators, research coordinators, research assistants, including those at other sites where the CRC IRB is the IRB of record, etc.) are considered research personnel or study staff. Faculty advisors serving as co-Investigators on student projects are also required to meet CITI training requirements.

The CRC IRB has selected the Collaborative Institutional Training Initiative (CITI) as the required online training program, which includes two training groups: Social & Behavioral Focus or Biomedical Focus. Individuals are responsible for choosing the Group that is most appropriate to their research. Within each Group there are several modules of training topics that must be completed to attain certification. Individuals are responsible for reviewing the ‘Other Modules’ (e.g. research with children, medical devices, etc.) and completing the ones that are appropriate for their research.

The IRB will check protocol submissions to confirm that investigators and research staff have completed the appropriate training requirements. Submissions cannot be approved until all staff listed on the protocol have completed those requirements.

Members of the BU workforce whose association with a research project is limited to providing University services (e.g. physical therapy, counseling, laboratory services, etc.), making appointments, or performing other tasks that they would otherwise perform as part of their non-research responsibilities are not considered research personnel and are not required to take human subject protection training.

#### **Alternatives to CITI training**

Individuals who complete non-CITI human subjects protection training will need to submit their certificates and completion reports to the IRB Office for an assessment of whether the training can be accepted in lieu of CITI. Prior to taking alternative trainings, it is advisable to check with the IRB Office to make sure the training will be an acceptable alternative to CITI. Note: the CRC IRB has approved the use of [Research Ethics for All](#) for community research partners with developmental disabilities who are engaged in human subjects research with CRC Investigators in lieu of CITI training.

#### **Recertification**

Certification in human subjects protection is required every 3 years. Individuals who complete CITI for initial certification will receive expiration/recertification reminders from CITI via e-mail 30 days and 7 days before their current certification expires. Individuals who complete alternative trainings to CITI will be responsible for keeping track of their training certification and recertification requirements and will be required to submit this documentation to the IRB office.

#### **Recently Transferred Investigators/Research Staff and those who are Outside of BU**

Individuals who have recently transferred from another institution, or who are outside of BU and working on

a BU research study and have completed human subjects protection training may submit their training certificate and completion report to the CRC IRB for review. The IRB will review the training to determine if it can be accepted in lieu of CITI training. If the IRB determines that the training is not adequate, the individual will be required to complete the CRC IRB CITI Training.

### **Good Clinical Practice Training**

Good Clinical Practice (GCP) training is required as part of the Responsible Conduct of Research requirements for post-doctoral trainees and their faculty mentors, as well as investigators and study staff of NIH-sponsored clinical trials and FDA regulated research. GCP is available via the CITI program.

### **In-Person or Video Conference Education and Training Options**

In addition to the online trainings, CRC offers, and at times may require, in-person training on human subjects research topics. The IRB Director and staff are available to conduct trainings or to talk with Investigators and staff about topics relevant to their research.

### **3.3 Investigator Conflicts of Interest**

All CRC Investigators and research staff must comply with the [BU Investigator Financial Conflicts of Interest Policy for Research](#) as well as Department of Health and Human Services regulations at [42 CFR Part 50 Subpart F](#) regarding financial conflicts of interest (COI).

The CRC IRB requires that Principal Investigators (PIs) confirm on their IRB Applications that all those responsible for the design, conduct, and/or reporting of the research, including at minimum, all key personnel in the funding application, have (a) completed the financial conflict of interest disclosure forms, (b) submitted them to the Financial Conflict of Interest (FCOI) office, and (c) completed FCOI training as required under the BU Policy. In addition, the PI must indicate on the relevant IRB Application if they, or any of the research staff, have disclosed a financial interest in the research submitted for review. The IRB Director serves as a non-voting member of the BU FCOI committee.

In reviewing IRB applications, if the PI indicates that there is a FCOI related to their research, the IRB Staff will contact the FCOI Office. If there is a FCOI related to the research, the IRB Staff will communicate this information to the IRB Director and the reviewer for the study, as appropriate. If the study is being reviewed by the convened IRB, the information will be presented at the convened meeting.

The FCOI Office will copy the IRB Office on any Management Plans related to an Investigator's human subjects research. The IRB may approve the research pending review of the Management Plan. If the FCOI Committee determines that there is no FCOI and/or no Management Plan is needed, the IRB may impose its own restrictions or requirements on the research and its investigators related to the conflict, however it may not remove any of those required by the FCOI Committee. The range of potential IRB actions may include the following, as well as other actions determined by the IRB at the time of review: No action, notification to research subjects, change in Investigator or research staff role, removal of the Investigator or research staff from the project, suspension of the project until the COI is resolved, or termination of the research project. The IRB Office will notify the PI directly of any IRB requirements regarding their FCOI.

## **4 Recruitment and Informed Consent Guidelines**

The IRB reviews an Investigator's proposed procedures for the recruitment and informed consent of research participants to ensure compliance with federal regulations. All materials to be used to recruit and consent research participants, including documentation of such consent, must be reviewed and approved by the IRB prior to implementation (e.g. recruitment advertisements, telephone scripts, direct mailings, consent forms and scripts, consent assessments, etc.). The IRB reviews these materials for consistency and accuracy with the protocol, to assure that non-coercive and voluntary language is included, and to ensure that confidentiality of participant information is maintained.

### **4.1 Recruitment Guidelines**

The CRC IRB is responsible for ensuring that the selection of research subjects is equitable. In order to fulfill this responsibility, the IRB will review and approve methods to recruit subjects to participate in research. Investigators are required to submit recruitment methods and recruitment materials to the IRB for review and approval prior to use. Investigators are required to include a full description of the recruitment plan (not just the name of the method) in the Initial Application or Amendment Form. The IRB will take into consideration the timing, location, and method of recruitment to ensure that the subjects are not unduly influenced to participate in the research. Investigators must provide their plans to recruit research subjects in their IRB applications and the materials to be used for recruitment (e.g. fliers, posters, online ads, phone scripts, etc.) must accompany the IRB application. The use of finder fees (offering or accepting fees for identification and referral of research subjects) and bonus payments to accelerate recruitment (tied to the rate or timing enrollment) are not ordinarily allowed.

#### **Recruitment Plans**

Recruitment plans should include the following information:

- How potential participants will be identified;
- How, by whom and where potential participants will be approached;
- How long after recruitment consent procedures will take place;
- Whether parties other than the Investigator and research personnel will recruit participants (e.g. health care center personnel).

#### **Advertisements**

The IRB will review the information included in the advertisement (copy of print advertising as well as scripts for audio/video) including the mode of communication. The IRB may approve documents that include "fill in the blanks" for such items as names, telephone numbers, times, etc. The IRB reviews advertising to ensure that it does not:

- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
- Include exculpatory language;
- Emphasize the payment or the amount to be paid, by such means as larger or bold type;
- Promise "free treatment" when the intent is only to say participants will not be charged for taking part in the investigation.

Advertisements are limited to the information prospective subjects need to determine their eligibility and interest, such as:

- The name of the researcher or research facility;
- The purpose of the research or the condition under study;
- Criteria (in brief) used to determine study eligibility;
- Benefits (in brief) to participants, if any;
- The time or other commitment required;
- The location of the research and the person or office to contact for further information.

### **Recruitment for FDA-Regulated Studies**

The IRB will review advertisements to ensure that they do not:

- Make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling;
- Use terms, such as “new treatment,” “new medication,” or “new drug,” without explaining that the test article is investigational;
- Allow compensation for participation in a trial offered by a sponsor to include a coupon for a discount on the purchase price of the product once it has been approved for marketing.

### **Recruitment from Primary and Secondary Schools and other External Organizations**

- **Schools:** For research being conducted in primary and secondary schools, the investigator is responsible for obtaining written approval of the appropriate official at the school and/or school district. This documentation must be submitted to the IRB.
- **External Organizations:** For research being conducted in organizations/institutions outside of Boston University (e.g. community organizations, workplace, clinics, etc.), the investigator is responsible for obtaining written approval of the appropriate official at the organization. This documentation must be submitted to the IRB.
- **Private lists and/or databases:** If investigators wish to contact subjects from privately held sources (e.g. lists, databases, etc.), they must provide written confirmation/permission from the owner of the source. In certain cases, the IRB may also ask for confirmation that the individuals included in the source have given permission to be contacted (e.g. the terms of use/agreement).

### **Recruitment of BU Employees, Students and Post Doctoral Trainees**

Investigators ordinarily will not be allowed to recruit, consent, or conduct study procedures on/with their own students or employees. There may be exceptions to these requirements if the research is not more than minimal risk, the investigator provides sufficient justification and provides appropriate assurances and protections for the students and employees, as applicable. Please see Section 11, Vulnerable Populations, for more information.

## **4.2 Payments to Research Participants**

Payments to individuals who participate in research is ordinarily offered as a form of appreciation for the individual’s time and effort in the research project. The CRC IRB must review and approve plans to compensate subjects. Investigators are required to include payment information in the IRB application and in the informed consent form. The CRC IRB does not have any specific requirement with regards to the amount or the form of payments. Payment is not considered to be a benefit of participating in a research study.

Payments may occur in one of the following ways:

- **Reimbursement:** Payments that are directly related to expenses that are incurred from participating in the research (e.g. payment for transportation, parking, childcare, meals, etc.).
- **Compensation:** Payments made to subjects for the time, effort and inconvenience of participating in the study (e.g. payment for time away from work or for the length of time required for study participation).
- **Gifts of appreciation:** Small payments, gifts, gift certificates, or other tokens give to subjects to thank them for their time and effort.
- **Incentives:** Payments, gifts, gift certificates that are intentionally used to encourage enrollment, continued participation, and/or motivation to perform study procedures.

The IRB will review the payment method and amount to determine that it meets the following criteria:

- The amount of payment, the proposed method and timing of disbursement is neither coercive nor presents undue influence;
- Credit for payment accrues as the study progresses and is not contingent upon the participant completing



the entire study;

- Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to participate in the study or stay in the study when they would otherwise have withdrawn;
- All information concerning payment, including the amount and schedule of payments is included in the consent document;
- Coupons and/or discounts on the purchase of investigational drugs, devices, or services once the drug, device, or service is approved or commercially available may not be used.
- If an investigator wants to impose a condition (e.g. completion of study task/s) in order for the subject to receive compensation, the IRB will determine whether the time and effort required of the subject to complete the study procedure/s justifies the condition.

### **Documentation of Payments**

It is recommended that investigators document when payments are made to subjects. The IRB QI Specialist is available to assist investigators by creating tools and logs for study documentation purposes.

### **Payments to Children**

For research involving children, the IRB will review the study to determine who (i.e. child subject, parent/guardian, or both) should receive the payment. In general, incentives should be provided to the child subject and compensation should be provided to the parent/guardian. The IRB will take into consideration the age and maturity of the child subject along with the circumstances of the study. The IRB will determine that the payment to the child subject is age appropriate.

### **Chance to Win**

The IRB may approve ‘chance to win’ methods if they meet the following criteria:

- The study is not greater than minimal risk;
- All subjects are eligible;
- All subjects have an equal chance of winning;
- If a subject withdraws, they are still eligible for the lottery/drawing (unless conditions are required to be eligible for the chance to win);
- The consent form must include the chances of winning;
- The value of the prize must be stated in the IRB Application and the consent form;
- The prize does not exert undue influence;
- If the investigator wants to impose a condition (e.g. completion of study task/s before the subject is eligible) then the IRB will need to determine whether the time and effort required of the subject to complete the study procedure/s justifies the condition.

### **Class Credit**

Class credit for student study participation may be allowed when the following criteria are met:

- There is an alternative means of obtaining course credit for those students who do not want to participate in the research study;
- The alternative means must be comparable in terms of time, effort, and educational benefit (e.g. participating in another research study, special project, additional readings, etc.);
- Subjects must be informed that they can withdraw at any time and course credit will be prorated.

### **Additional BU Policies on Payments**

Investigators are required to comply with applicable Boston University policies related to payments, including Sponsored Programs Post Award Financial Operations Human Subjects Payments and Taxability of Gifts, Prizes, and Awards to Employees.

## **4.3 Informed Consent Guidelines**

The regulations at 45 CFR § 46.116 stipulate that legally effective informed consent of the research participant (subject) or the subject's Legally Authorized Representative (LAR) must be obtained prior to their involvement in 'human subjects' research. The regulations provide criteria for the information that must be communicated during the informed consent process, how informed consent should be documented, as well as the circumstances under which informed consent - or elements of informed consent - may be waived.

Informed consent must:

- Be in a language understandable to the subject/LAR;
- Include information that a reasonable person would want to have in order to make an informed decision about whether to participate in the research;
- Not include exculpatory language through which the subject/LAR is made to waive or appear to waive either party's legal rights, or releases or appears to release the investigator, sponsor, institution or its agents from liability for negligence;
- Provide adequate opportunity for the subject/LAR to read and discuss the informed consent form before it is signed;
- Ordinarily be written at an 8th grade reading level (though, this is dependent on the study population);
- Define medical, technical or professional terminology and other jargon in lay terms;
- Be written in a context that is easy to follow (e.g. subject headings, short and concise sentences, numbering or bullet points, timelines for complex procedures, etc.);
- If subjects will be paid, include the amount, schedule of payment and any requirements to obtain payment;
- If signed consent is being obtained, include the date of consent by the subject/LAR and signature lines for the subject/LAR and researcher who administered consent;
- If identifiable information will be sent to central University offices (e.g. Accounts Payable, Post Award Financial Operations, etc.), there is a disclosure statement;
- If a student is the PI, the PI is identified as a student and their Faculty Advisor's name and contact information is also included;
- Request consent for any optional procedures (e.g. audio/video recording, future contact, etc.)
- Be presented to participants/LARs by appropriate research team members who have the experience and knowledge about the research and can answer the questions or concerns of prospective participants;
- Include the IRB's contact information;
- Begin with a concise and focused presentation (summary) of the key information, in sufficient detail, that is most likely to assist a prospective subject/LAR in understanding the reasons why one might or might not want to participate in the research study, including: the purpose of the study, the time involved for study participation, the study procedures to be conducted, and any risks of participating in the study.

#### **4.4 Required Elements of Informed Consent [45 CFR 46.116(b) and 21 CFR 50.25]:**

The following elements must be included when obtaining informed consent:

- (1) 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;
- (2) A description of any reasonably foreseeable risks or discomforts to the subject;
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and 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;

- (7) 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;
- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;
- (9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
  - (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility, OR
  - (ii) A statement that the subject's information or biospecimens collected as part of research, even if identifiers are removed, will not be used or distributed for future research studies.

**Additional Elements of Informed Consent under 45 CFR 46.116(c), as appropriate:**

When appropriate, one or more of the following elements of information must also be provided to each subject:

- (1) 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 (e.g. when the research involves investigational test articles or drugs or other procedures in which the risks to the participants are not well known) (DDHS and FDA);
- (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- (3) Any additional costs to the subject that may result from participation in the research;
- (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
- (6) The approximate number of subjects involved in the study;
- (7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
- (8) A statement regarding whether clinically relevant results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
- (9) For research involving biospecimens, whether the research will (if known) or might include genome sequencing (i.e. sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Note: at this time, the CRC IRB does not allow Broad Consent [45 CFR 46.116(d)].

#### **4.5 FDA Informed Consent Requirements**

If the research is regulated by the FDA, the IRB will confirm the following:

- A statement noting the possibility that the FDA may inspect the records will be included in the consent form;
- If the results of the research will be posted on [clinicaltrials.gov](http://www.clinicaltrials.gov), the following statement will be included in the consent form: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."
- For research that involves a drug or device and researchers plan to use BU REDCap for any data collection, including e-consent, the study must comply with [FDA 21 CFR Part 11 requirements for electronic records and signatures](#). An overview of the process the clinical investigation team must follow

can be found [here](#).

#### **4.6 Documentation of Informed Consent**

Unless the requirement for documentation of consent is waived by the IRB, informed consent must be documented by a written informed consent form (ICF) approved by the IRB and signed, including in an electronic format, by the subject/LAR. A copy of the consent form must be given to the person signing the ICF. For studies that are deemed greater than minimal risk and/or are reviewed at a convened IRB meeting, use of the CRC IRB Informed Consent Template with study participants is required; use of the Template is strongly advised and encouraged for all other studies.

The ICF may be one of the following:

1. A written consent document that embodies the basic and required additional elements of informed consent. The Investigator shall give either the subject/LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject/LAR; or
2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject/LAR and that the key information required by 45 CFR 46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. When this method is used:
  - The oral presentation and the short form written document should be in a language understandable to the subject;
  - There must be a witness to the oral presentation;
  - The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary);
  - The short form document is signed by the subject;
  - The witness must sign both the short form and a copy of the summary;
  - The person obtaining consent must sign a copy of the summary; **and**
  - A copy of the signed summary must be given to the subject or representative, in addition to a copy of the short form.

#### **4.7 Approval of Consent Materials**

The consent form/consent script/information sheet will be evaluated by the IRB Reviewer. The IRB Reviewer will complete the Consent Form Review Checklist. Approved consent materials reviewed by expedited or full board procedures will be stamped with study approval and expiration dates by the Analyst. The IRB Approval notice will indicate when waivers or alterations of informed consent have been granted.

#### **4.8 Informed Consent by Legally Authorized Representatives**

If a potential participant cannot provide consent, then a surrogate decision maker, or LAR, must consent to the individual's participation in the research. The federal regulations at 45 CFR 46.102(i) define "*legally authorized representative*" as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research". It further states that if there is no applicable law addressing this issue, "legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research." Under Massachusetts law, this means the consent must come either from the legal guardian of the participant, or from the participant's health care agent (either as appointed under the Massachusetts health care proxy law, or as identified by a health care provider under the common law for obtaining consent to the provision of medical care and associated procedures).

The CRC IRB will allow consent to be obtained from the following persons, in the following order:

- A court-appointed guardian who has clear authority to make health care decisions;

- A person designated as a health care agent under a valid health care proxy, with express authority to make health care decisions;
- A durable power of attorney with express authority to make health care decisions;
- A family member: including a competent spouse, adult child, or competent parent.

#### **4.9 Subjects who are Non-English Speaking or have Limited Understanding of English**

The federal regulations stipulate that consent materials must be provided to prospective subjects/LARs in a language that is understandable to them. For Investigators who enroll non-English speakers (or those with a limited ability to understand or read materials in English), materials to be used with or by these subjects must be translated into a language that is understandable to them. Written consent documents, regardless of the language in which they are written, must contain all the elements of consent.

In lieu of a translated consent form, the federal regulations at 45 CFR § 46.117(b)(2) permit an Investigator to verbally present the information required to allow a participant to make an informed judgment about participation in research, provided that there is a witness to the verbal presentation and the participant is given a written summary of the presentation, as well as a copy of the short form written consent document (stating that the elements of consent have been presented verbally). When this procedure is used with potential participants/LARs who do not speak English:

- The verbal presentation and the short form written document should be in a language understandable to the potential subjects/LARs;
- The witness should be fluent in both English and the language of the subject/LAR. Investigators must determine whether the translator is appropriately trained to also serve as a witness to the consent process and if not, a translator *and* a witness must be retained;
- The approved English language informed consent document may serve as the summary, as long as it is read by the witness in the language understandable to the subject/LAR;
- At the time of consent:
  - the short form document should be signed by the subject/LAR;
  - the summary should be signed by the person obtaining consent as authorized under the protocol;
  - the short form document and the summary should be signed by the witness.

A copy of non-English language materials to be used with or by subjects/LARs should be submitted to the IRB, with an accompanying Translation Attestation Form. The Translation Attestation Form is intended to provide an alternate to back-translations of translated documents, confirm that each appropriate document has been translated, and to verify the documents' authenticity to the English version of the IRB approved materials (e.g. consent, data collection forms).

#### **4.10 Witness to the Consent Process**

A witness is required in the following circumstances:

- If the IRB approves the use of the "short form" (see previous sections); and
- When a participant cannot read, and the consent document must be read to him or her.

The witness is required to sign and date the consent form. The witness signature attests that the information in the consent form (and other written documents, as applicable to the research) was accurately explained to and understood by the participant/LAR, and that the informed consent was given freely. The witness should be independent of the research. Translators for non-English speaking participants/LARs may be used as witnesses, however Investigators must determine whether the translator is appropriately trained to assess the attestation standard, and if not, a translator and a witness must be retained.

#### **4.11 Waivers and Alterations of Informed Consent**

The IRB may waive the requirement for the investigator to obtain consent or alter some or all of the elements of consent if the IRB finds that one of the options below applies.

**(1) Waiver or Alteration Involving Public Benefit and Services Programs [45 CFR 46.116(e)]**

In order for an IRB to waive or alter consent as described in this section, it must find and document:

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

**(2) General Waiver or Alteration of Consent [45 CFR 46.116(f)]**

In order for an IRB to waive or alter consent as described in this section, it must find and document:

- The research involves no more than minimal risk to the subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- Whenever appropriate, the subjects/LARs will be provided with additional pertinent information after participation.

Investigators may be asked to provide justification or additional information to support that the above criteria are satisfied.

**(3) Screening, Recruiting, or Determining Eligibility**

The IRB may approve a research study in which the investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects with the informed consent of the prospective subject/LAR without granting a waiver, if either of the following conditions are met:

- The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, OR
- The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

**(4) Waivers and Alterations of Consent for FDA-Regulated Studies**

The IRB can alter, some or all of the elements of informed consent, or waive the requirements to obtain informed consent when it finds and documents that:

- The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The clinical investigation could not practicably be carried out without the waiver or alteration
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation. If the investigator is not providing this information, they must provide the rationale for why it is not necessary to provide additional information after participation.

**(5) Waiver of Documentation of Consent [45 CFR 46.117(c)]**

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects when it finds that:

- That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject

(or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

- 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; **OR**
- If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

#### **4.12 Posting of Clinical Trial Consent Forms**

For research funded by the NIH, there is a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. This requirement may be satisfied by either the awardee or the Federal department or agency. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g., confidential commercial information), the department or agency may permit or require redactions to the information posted. An acceptable public federal website for posting clinical trials is [clinicaltrials.gov](http://clinicaltrials.gov).

## 5.0 IRB Review of Research involving Human Subjects

Activities that meet the federal definition of ‘research’ at 45 CFR 46.102(l) and ‘human subjects’ at 45 CFR 46.102(e) require IRB review and approval. The CRC IRB is responsible for determining whether activities and projects meet these definitions and when or whether IRB review and approval is required. An IRB Member who is designated as an expedited reviewer by the IRB Chair may make these determinations. The IRB has the authority to approve, require modifications to secure approval, and to disapprove research activities being conducted by members of the BU CRC. Officials of Boston University cannot approve research with human subjects that has not been approved (or that has been disapproved) by the IRB.

### Defined Terms

**Research** is defined as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. To be considered a “systematic investigation,” the concept of a research study ordinarily:

- Attempts to answer research questions (for example, a hypothesis)
- Is methodologically driven (data/information are collected in an organized/consistent way), and
- Conclusions are drawn from the results.

To be considered “generalizable knowledge,” the activity ordinarily includes the following concepts:

- The information gained contributes to a theoretical framework of established knowledge,
- Results are intended to be generalized to a larger population beyond the site of data collection or population studied, and
- Results are intended to be replicated in other settings.

The following activities are deemed NOT to be research:

- Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

**Classroom and other University Activities** are not ordinarily considered human subjects research if there is no intent to develop or contribute to generalizable knowledge and the activities are being conducted for educational purposes only. If the faculty member is unsure if the activity requires review, they should contact the IRB.

University activities that ordinarily will require IRB review include the following (though not exhaustive):

- Pilot studies that involve human subjects
- Master’s theses and dissertations involving research with human subjects
- Use of identifiable information from medical records, student records, employment records, or other private sources
- Collection and analysis of data about human subjects through interaction or intervention with subjects,



such as surveys, interviews, focus groups, cognitive testing, etc.

University activities that ordinarily do not require IRB Review include the following (though not exhaustive):

- Data collected for internal departmental or administrative purposes, such as teaching evaluations, student performance data, etc.
- Studies of institutions, policies, or processes (collection or analysis of data on “things” rather than information collected from people about themselves)
- Activities designed solely for quality improvement or evaluation of a particular program, course, etc.
- Oral histories or biographies (unless data will also be used to contribute to generalizable knowledge)
- Training activities (unless the training activity is conducted for research purposes)
- Single case studies

**Human Subject** is defined as a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

To meet the definition of a ‘human subject’, the following must apply:

- The ‘subjects’ are currently alive,
- The information to be collected is about the ‘subjects’ (e.g. personal information about the individuals), and:
- Information/biospecimens are collected by an intervention (physical procedures and manipulations of the subject or the subject’s environment for research purposes) or an interaction (communication or interpersonal contact between investigator and subject) AND the Investigator uses, studies or analyzes the information/biospecimens, OR
- The Investigator obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

**Engagement in Research** occurs when CRC “employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.” Additionally, the CRC is considered ‘engaged’ in the research if the Institution receives a direct award from DHHS for the research, regardless of whether the activities will take place at CRC or another institution. The engagement of CRC in non-exempt human subjects research requires CRC IRB review and oversight of the research, or the reliance of CRC on an external IRB.

### **Submission of Materials to the IRB**

To receive an official determination of whether a project is Research Involving Human Subjects, Investigators should complete and submit the Research with Human Subjects Determination Form and submit it along with any supporting materials, such as a grant or contract supporting the research, data collection forms, and other materials (e.g. assessments, questionnaires, etc.) to be used in the project. Informal inquiries into whether IRB review and approval may be needed do not require submission of the Determination Form.

### **IRB Determination and Investigator Notification**

When received, the IRB Coordinator assigns the Determination Form a study number, enters it into the tracking system, and screens the Form for completeness. If information/material is missing, the IRB Coordinator will request this information/material from the Investigator or their designee. The Coordinator will provide the file to the IRB Analyst responsible for the reviews of the submitting PIs Department. The IRB Analyst will review the Form to determine if the activity meets the definitions of ‘research’ and ‘human subjects’. If the IRB Analyst requires additional information, they will contact the PI via e-mail and review the PI’s response upon receipt. If the PI does not respond within 60 days, the determination inquiry will be withdrawn. If the IRB Analyst does not believe that the materials received are sufficient, the Analyst may

request that the PI make further clarifications and/or revisions. This process will continue until a determination can be made. Once the IRB Analyst makes the determination, the Form with the signed/dated determination will be sent back to the Investigator as official documentation, ordinarily within 5 business days.

## **5.1 IRB Review of Grants and Contracts Supporting Human Subjects Research**

Under the Revised Common Rule, effective January 19, 2019, IRBs are not required to review Department of Health and Human Services (DHHS/HHS) funding applications supporting research with human subjects. Instead, certification is required when the research is supported by a federal department/agency and not otherwise waived under 45 CFR 46.101(i) or exempt under 45 CFR 46.104. For such research, the CRC IRB shall certify that each proposed research study covered by the CRC Assurance has been reviewed and approved by the IRB. The exception to this rule includes specific DHHS/NIH policy requirements for certifications of grant concordance with the research protocol and/or the informed consent of original study participants for Genome-Wide Association Studies (GWAS), Genomic Data Sharing Plans, (GDS), and other studies requiring such certification.

Grants and contracts supporting human subject research should provide adequate information for research participants about items such as compensation or treatment for any injuries that might be incurred from the research, coverage of non-reimbursable research items and services, compensation for participation (e.g. remuneration or transportation), research materials and/or study interventions (e.g. the drug, device or other product being investigated), and other items as appropriate.

Federal regulations at 45 CFR 46.122 stipulate that no federal funds may be expended for human subjects research unless the requirements of the regulations have been met. Principal Investigators may conduct human subjects research once they have provided the Sponsored Programs Office with evidence of current and relevant CRC IRB approval. BU is aware that certain types of grants, contracts, and agreements are applied for and awarded with no definite plans for the involvement of human subjects. These may include institutional awards (where the selection of projects to fund is the institution's responsibility), training grants (activities involving human subjects are not yet selected), and projects that will not enroll human subjects until the completion of instruments, prior animal studies, etc. The IRB is not required to review such applications prior to the Investigator receiving the funds, however no human subjects research may occur until the project has been reviewed and approved by the IRB (45CFR46.118). Grants that are awarded without the intent to involve human subjects, but later propose to involve human subjects, must be submitted for IRB review and approval prior to the enrollment of human subjects (45CFR46.119).

The CRC IRB Office will obtain from the Investigator (or relevant BU administrative offices, as necessary) copies of grants/contracts/agreements supporting human subjects research to review with the relevant protocol/IRB application. Investigators whose grants or contracts are pending at the time of IRB submission should submit the funding application and indicate the status of the award on the IRB application. Grants and contracts awarded after IRB approval should be submitted by the Investigator to the IRB as amendments.

Agreements, such as those with industry and clinical trial agreements, that involve human subjects must include the following, as applicable:

- When there is risk for potential injury, who will provide care and who is responsible for the payment of care. There is no requirement to pay for potential injuries, however the contract should specify this information. The consent document should be consistent with the contract and describe the risks, whether there will be payment or treatment provided in case of injury, and who will provide this payment or treatment. If there is no payment or treatment available, this should be clearly explained.
- If the contract or the research includes monitoring of research sites, the sponsor must promptly report to the Investigator to enable the Investigator to report to CRC IRB any findings that could affect the safety of participants or influence the conduct of the study. In this circumstance, 'promptly' means within 3 working days of discovery of any unanticipated problems involving risks to subjects or others, or serious

deviations from the protocol. Minor deviations must be reported within 20 working days. Please see the definitions of unanticipated problems and major versus minor deviations in the CRC IRB policies.

- As applicable, the timing of development of the data safety monitoring plan (DSMP), the review and approval of the DSMP by the CRC IRB, and the frequency of when data safety monitoring reports will be submitted to the CRC IRB by the Investigator. DSMPs developed by (or with) the sponsor must be submitted to the CRC IRB to review with the protocol. If the DSMP is not developed at the time of initial submission to the IRB, when available it must be submitted as an amendment. Data safety monitoring reports must be submitted by the Investigator to the CRC IRB within 30 days of its availability, and promptly (within 3 working days) in the event of discovery of any unanticipated problems involving risks to subjects or others, or serious deviations from the protocol. Please see the definitions of unanticipated problems and major versus minor deviations in the CRC IRB policies.
- A plan for communicating findings to Investigators and/or the CRC IRB that directly affects participant safety and that have been discovered after a study has closed. This discovery should be reported promptly.

IRB analysts and IRB members must review the grants, contracts and agreements that support research involving human subjects with the protocol/IRB application. In its review of contracts/agreements, if IRB analysts/members identify missing requirements or other issues with industry contracts/agreements, they will notify the appropriate BU Administrative Office. Any special interests or conflicts of interest of the Sponsor and/or Investigator must be disclosed by the Investigator in the IRB application and in the Informed Consent Form and reviewed by the IRB as part of the IRB review and approval process. Industry contracts/agreements are reviewed/approved by BU Office of Industry Engagement and any conflicts must go through review by the BU FCOI Committee.

## **5.2 Scientific Review**

In accordance with 45 CFR § 46.111(a)(1) and [21 CFR § 56.111\(a\)\(1\)](#), the IRB considers whether risks to participants are minimized in part by evaluating whether the research procedures are consistent with sound research design and necessary and sufficient to answer a research question of importance (i.e., one that has not been answered or that requires additional confirmation). Clinical research reviewed by the CRC IRB may have received prior scientific review by entities such as an NIH Study Section, FDA Review Committee, or an industry-sponsored Review Committee. The IRB will consider these prior reviews as an indication that the scientific research design is sound, but these reviews do not release the IRB of its responsibility for scientific evaluation of the study protocol. If the IRB, staff and/or Chair, or IO, does not believe the IRB membership has the expertise required to evaluate the scientific question or proposed research methods, a consultant may be sought to review the protocol. A research protocol will not be approved unless it meets scientific standards, as well as ethical standards and regulatory criteria for approval.

## **5.3 Approval Criteria**

In accordance with criteria at 45CFR46.111:

- (a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
  - (1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
  - (2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should 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). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
  - (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the

purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

- (4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and when applicable, [21 CFR 50.20](#).
  - (5) Informed consent will be appropriately documented or appropriately waived, in accordance with, and to the extent required by 45 CFR 46.117 and when applicable, [21 CFR 50.27](#).
  - (6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
  - (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
  - (8) For the purposes of conducting the limited IRB review as required by 45 CFR 46.104(d)(7), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations: (i) Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of 46 CFR 46.116(a)(1)-(4), (a)(6), and (d); (ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with 45 CFR 46.117; and (iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. **Note:** because the CRC IRB does not offer the use of Broad Consent at this time, items 8(i)-(ii) above do not apply to CRC Investigators.
- (b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

#### **5.4 Exempt Research**

Research activities that meet the categories defined by the federal regulations at 45 CFR 46.101(b) and 21 CFR 56.104(d) may qualify for exemption. The CRC IRB is responsible for determining if a research activity is exempt. Research may be exempt from the requirements if the activities are not greater than minimal risk and fall into one of the following categories:

1. Research conducted in established or commonly accepted educational settings, involving normal education practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular or special educational instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving only the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior (including visual or auditory recording, if at least one of the following criteria is met:
  - (i) Information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
  - (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability; or be damaging to the subjects' financial standing, employability, educational advancement, or reputation. OR
  - (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can be readily ascertained, directly or through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).

When limited IRB review is used to approve the research, the IRB confirms that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of their data.

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) audiovisual recording if the subject prospectively agrees to the intervention and information collection at least one of the following criteria is met:
    - (A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    - (B) Any disclosure of the human subjects' responses outside of the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; OR
    - (C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly through identifiers linked to the subjects, and the IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7).
  - (ii) For the purposes of this provision, benign behavioral interventions are brief in duration, harmless, painless, and not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has not reason to think the subjects will find the interventions offensive or embarrassing. Examples include playing an online game, solving puzzles under various conditions, and deciding how to allocate a nominal amount of received cash between themselves and someone else.
  - (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.
4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
    - (i) The identifiable private information or identifiable biospecimens are publicly available
    - (ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify the subjects
    - (iii) The research involves only information collection and analysis involving the investigator's use of identifiable information when that use is regulated under 45 CFR parts 160 and 164 ('HIPAA'), subparts, A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b) OR
    - (iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and if, applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C 3501 et seq.
  - 5 Research and demonstration projects which are conducted by or otherwise subject to the approval of federal department or agency heads (of the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects, and which are

designed to study, evaluate, or otherwise examine: public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting agreements, cooperative agreements, or grants. Exempt projects also include waivers or otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

- (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

[Reserved]

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 FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Note: The CRC IRB will not implement Categories 7 and 8 as described in 45 CFR 46.104(d)(7) and 45 CFR 46.104 (d)(8).

Research activities that cannot be exempt:

- Research that involves prisoners;
- Survey or interview procedures or observations of public behavior involving children except for research involving observation of public behavior when the investigator does not participate in the activities being observed;
- FDA regulated research unless it qualifies under Category 6.

### **Exemption Review Process**

If the PI believes that a study meets the criteria for exemption, they must complete the Exempt Application and submit it with all applicable documents (consent/ information sheet, recruitment materials, questionnaires, surveys, etc.) to the CRC IRB Office via email. When received, the IRB Coordinator assigns the application a study number, enters it into the tracking system, and screens the Application for completeness. If information/material is missing, the IRB Coordinator will request this information/material from the Investigator. The Coordinator will provide the file to the IRB Analyst responsible for the reviews of the submitting PIs Department.

The IRB Analyst will review the Application to determine if the study falls into one of the exemption categories as defined in 45 CFR 46.101(b) and 21 CFR 56.104(d). In addition, the IRB Analyst will determine that the study meets the ethical standards of the CRC IRB using the following criteria: The research involves no more than minimal risk to subjects, if subjects will be enrolled, selection is equitable, if there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data, if there are interactions with subjects, there will be a consent process that will disclose such information as: the activity involves research, the purpose of the research, a description of the procedures, the amount of time required for the research, how confidentiality of data will be maintained, risks and benefits of participating in the study, participation is voluntary, name and contact information for the Investigator, contact information for the CRC IRB, a description of the provisions to maintain the privacy interests of subjects.

If the IRB Analyst requires additional information or modifications, they will contact the PI via e-mail and review the PI's response upon receipt. If the PI does not respond within 60 days, the study will be withdrawn. If the IRB Analyst determines that the revisions are inappropriate or insufficient, the Analyst may request that the PI make further revisions. This review and revision process will continue until the research is either determined to be exempt or moved to expedited or convened IRB review.

Once the IRB Analyst determines that the study qualifies for exemption, a letter will be sent to the PI notifying them of the determination ordinarily within 5 business days. The letter will include the specific category of exemption. Once a study is determined to be exempt, annual reviews are not required. If the IRB Analyst determines that the study does not qualify for an exemption, the study will be referred for expedited or convened IRB review, as applicable.

## **5.5 Expedited Review of Research**

Under 45 CFR 46.110 and 21 CFR 56.110, expedited review procedures are allowed for certain categories of research involving no more than minimal risk and for minor changes in approved research. The Secretary of the Department of Health and Human Services (DHHS) has published a list of research activities in the [Federal Register](#) that may be reviewed by the IRB by expedited procedures, as follows:

- A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
- B. The categories in this list apply regardless of the age of subjects, except as noted.
- C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- D. The expedited review procedure may not be used for classified research involving human subjects.
- E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.
- F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review:
  - 1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    - (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
    - (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
  - 2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
    - (a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
    - (b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner, (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction, (c) permanent teeth if routine patient care indicates a need for extraction, (d) excreta and external secretions (including sweat), (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue, (f) placenta removed at delivery, (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor, (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques, (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings, (j) sputum collected after saline mist nebulization.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy, (b) weighing or testing sensory acuity, (c) magnetic resonance imaging, (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography, (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
8. Continuing review of research previously approved by the convened IRB as follows:
  - (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - (b) where no subjects have been enrolled and no additional risks have been identified; or
  - (c) where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) 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.

In compliance with 45 CFR 46.110(b)(1) and 21CFR56.110, the CRC IRB uses the expedited review procedure to review the following:

- (i) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,
- (ii) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.



The CRC IRB considers a proposed change to be ‘minor’ if it:

- Does not significantly alter the risk:benefit assessment of the protocol;
- Does not significantly affect the safety of research participants, such as adding significant medical, social or psychological risks;
- Does not involve the addition of procedures, interactions or interventions that are not otherwise eligible for expedited review;
- Does not involve the addition of a vulnerable population not otherwise eligible for expedited review; and
- Does not significantly alter the scientific question or quality of the study.

(iii) Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C). Note: because the CRC IRB does not offer the use of Broad Consent at this time, exemptions (d)(7) and (8) are not available to HSL Investigators.

(iv) The IRB must document the rationale for a determination that research appearing on the expedited review list published in the Federal Register is more than minimal risk.

### **Expedited Review Procedures**

The IRB Chair designates experienced IRB members to review research that meet expedited criteria. An experienced member is a member who has served on the IRB for at least six months, has received training relative to the expedited review categories, and has the appropriate background and knowledge to conduct the review. If the research involves prisoners, the IRB Prisoner Representative must serve as one of the reviewers. The Expedited Reviewer may make the following determinations: 1) approval, 2) modifications required for approval, or 3) referral to the convened IRB for review. The Expedited Reviewer may not disapprove research by expedited procedures; disapproval may only be conducted by the convened IRB. Research that is approved using the expedited review process will be included in the meeting packet for the next scheduled convened IRB meeting.

If the PI believes that a study meets the criteria for expedited review, they must complete the Expedited/Full Board IRB Application and submit it with all applicable documents (consent/ information sheet, recruitment materials, questionnaires, surveys, etc.) to the CRC IRB Office via email for review. When received, the IRB Coordinator assigns the application a study number, enters it into the tracking system, and screens the Application for completeness. If information/material is missing, the IRB Coordinator will request this information/material from the Investigator. The Coordinator will provide the file to the IRB Analyst responsible for the reviews of the submitting PIs Department.

When the Reviewer:

- Requires additional information or modifications, they will contact the PI via e-mail and review the PI’s response upon receipt. If the PI does not respond within 60 days, the study will be closed/withdrawn. If the Determines that the revisions are inappropriate or insufficient, they may request that the PI make further revisions. This review and revision process will continue until the research is either approved or sent to the convened IRB for review (disapproval of research is permitted only by the convened IRB).
- Determines that the study requires review by an IRB member with specific scientific expertise, that member will be asked to serve as a Secondary Reviewer.
- Determines that the study is appropriate for approval, an approval letter will be sent to the PI inclusive of the specific category of expedited review, the approval date, and the annual check-in date.
- Determines that the study qualifies for review by Exempt procedures, the study will be approved under specific Exempt category(ies).
- Determines that the study does not qualify for review by expedited procedures, the study will be referred for Full Board review.

If the PI has concerns about the IRB’s decision or recommendations, they may address their concerns to the IRB in writing.

IRB staff will communicate the determination in writing (as well as the rationale for the decision) to Investigators ordinarily within 5 days of review.

## **5.6 Review by the Convened IRB**

All non-exempt human subjects research that is not eligible for expedited review will be reviewed at a convened IRB meeting. For a convened meeting to occur, a majority of the IRB members must be present, including at least one member whose primary concerns are in nonscientific areas. The IRB may invite the PI and consultants to attend the meeting to provide information and/or answer questions. Research may be approved at a convened meeting with the approval of a majority of those members present.

PIs who believe their study meets the criteria for review at a convened meeting must complete the Expedited/Full Board Application and submit it with all supporting documentation (e.g. Informed Consent Form, recruitment materials, questionnaires, surveys, interview questions, supplemental IRB forms, etc.). All IRB applications are pre-reviewed by the IRB Coordinator and an IRB Analyst before going to the convened IRB for final review.

- The IRB Application is received by the IRB Coordinator who assigns a protocol number and enters the study into the IRB tracking system. The Coordinator conducts an administrative pre-review to check for missing or incomplete documents. Incomplete submissions are returned to the Investigator.
- The IRB Analyst will conduct a review of the Application by completing the appropriate Reviewer Worksheet. This review is focused on ensuring that the Application complies with IRB policies and the regulatory criteria for approval. The Analyst will provide the Investigator with questions that need to be addressed prior to the convened meeting. The Analyst will also start to complete the appropriate Approval Checklist. The Reviewer Worksheet, Approval Checklist, and any other correspondence with the PI will be provided to the IRB members for their review prior to the convened meeting.

### **IRB Meeting Document Distribution:**

Meeting documents are posted to a password-protected site ordinarily one week prior to the meeting date. IRB members, IRB staff, Executive Director of Research Compliance and the Institutional Official (IO) are the only individuals who have access to these materials. These individuals and any invited guests receive an agenda and are notified via email when the documents have been posted. The meeting materials include a report of items approved in the previous month via expedited procedures, those determined to be exempt or not human subjects research, expedited incidents/events, and the minutes from the previous convened meeting. Meeting materials will be projected during the meeting for each review. This is true for in-person as well as video-conferenced meetings.

### **IRB Actions:**

The possible actions that can be taken by the IRB are:

- **Approve:** The study is approved as submitted and meets approval criteria as outlined in 4.9. The date of approval will be the date of the meeting (unless a continuing approval is granted within 30 days of the previous approval date). The approval period will not be longer than one year unless the IRB determines that more frequent review is necessary.
- **Contingent Approval/Requires Modifications:** If the IRB determines that all regulatory criteria have been met in accordance with 45 CFR 46.111 and 25 CFR 56.111 the IRB may approve the study pending specific minor revisions. In this instance, the IRB may require that the PI do one or any of the following: (a) make specified changes to one or more of the research documents, (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or (c) submit additional documents. The response to these modifications can be reviewed by the Primary Reviewer, Secondary Reviewer, IRB Chair, and/or IRB Assistant Director and does not need to be reviewed at a subsequent convened meeting. The date of approval will be the date that the conditions were met. The approval period will not be longer than one year and is determined on risks to study participants.
- **Defer:** If the IRB does not have sufficient information to determine that all of the regulatory criteria have

been met in accordance with 45 CFR 46.111 and 25 CFR 56.111, the IRB will defer approval of the study. The PIs response to the deferral and any revised study documents will be reviewed at a subsequent convened meeting.

- **Disapprove:** The study cannot be approved as submitted. This occurs when the IRB determines that the risks outweigh the benefits or value of knowledge to be gained, if there is insufficient information to approve the study, if there are significant ethical, methodological, or scientific concerns, or if it does not meet regulatory criteria for approval. If the IRB disapproves a study, the notification to the PI will include a statement of the reasons for the decision to disapprove the study. An Investigator may appeal this decision by submitting the appeal in writing to the IRB Assistant Director and IRB Chair. The appeal will be reviewed by the IRB at a convened meeting.

Research approved by the IRB may be subject to approval by other offices or individuals within Boston University. This may include but is not limited to: Vice-President and Associate Provost for Research, Institutional Official, General Counsel, Export Controls, Radiation Safety, Institutional Biosafety Committee, International Office, etc.

### **Review Process**

The Primary Reviewer will present a summary of the protocol, followed by their comments. The Secondary Reviewer will present their comments after the Primary Reviewer. The IRB Chair/Vice-Chair then opens the discussion to all IRB members. The IRB must determine that the regulatory criteria for approval, as outlined in 4.9, are met. Following the discussion, the Primary and Secondary Reviewers will suggest an action. The IRB Chair/Vice-Chair will ask for a vote on the suggested action. The vote is taken and recorded. An action is confirmed when the majority of the members present agree on the action (e.g. approve, defer, etc.). The PI will be notified of the IRB determination via email, ordinarily within 5 business days.

### **Multisite Research**

When the BU CRC is the IRB of record and the BU PI is the lead researcher of a multi-site study, the IRB will evaluate whether the management of information that is relevant to the protection of subjects is adequate. This will include the communication plan for noncompliance, unanticipated problems, interim results, protocol modifications, adverse events, subject complaints, and other events related to the conduct of the study.

### **Notification to the Institutional Official**

The IO is copied on meeting notices to the IRB members and has access to all the meeting documents. These documents include the meeting agenda, administrative and study-related document, minutes, and the report of expedited and exempt reviews.

### **Review Period**

The IRB will determine the approval period based on the risk to subjects. Continuing review will be conducted at intervals appropriate to the degree of risk but not less than once per year (annually). The IRB may determine that continuing review must occur more frequently than annually. Continuing review may be required more frequently when:

- The research may involve significant risks to subjects;
- The research involves novel interventions;
- The PI has a history of non-compliance;
- The IRB Application required significant revisions or complicated procedures;
- The PI is new to research.

## **5.7 Research Requiring Review More Often than Annually**

While most full board approvals are granted for one year, there are projects that may require more frequent review. When deciding on appropriate intervals for continuing review, the convened IRB considers factors such as:

- The nature of any risks posed by the research project;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the Investigators in conducting research;
- The IRB's previous experience with the Investigators (e.g., compliance history, previous prior complaints from subjects about the research or then Investigator);
- The projected rate of enrollment; and
- Whether the research project involves novel interventions.

When the IRB has determined that more frequent than annual review is warranted, it will document its determination in the minutes of the meeting.

#### **Investigator Notification:**

IRB staff will communicate the determination in writing (as well as the rationale for the decision) to Investigators ordinarily within 5 days of review.

### **5.8 Single IRB Review, Ceded Review and Reliance Agreements**

To avoid duplication of effort, and to comply with Federal policies for single IRB review of multi-site and cooperative research, the CRC IRB will either accept review responsibilities on behalf of another institution or rely on the review of an external IRB; this process is called an IRB reliance, or ceded IRB review.

#### **Defined Terms:**

**IRB Authorization Agreement/Reliance Agreement:** the agreement that documents respective authorities, roles, responsibilities, and communication between an institution/organization providing the ethical/IRB review and a participating site relying on the single IRB.

**Cooperative Research:** Research projects that involve more than one institution.

**Multi-Site Study:** A multi-site study uses the same protocol to conduct non-exempt human subjects research at more than one site.

**Participating Site/Relying Institution:** A Participating Site in a multi-site study is a domestic entity that will rely on the single IRB to carry out the site's IRB review of human subjects research for the multi-site study.

**Reliance/Cede Review:** The act of transferring IRB review and oversight to another IRB

**Reviewing IRB:** The IRB that conducts the IRB review.

**Single IRB (sIRB):** The IRB of record that has been selected to carry out the IRB review requirements for a multi-site or cooperative research study. The IRB may also act as the Privacy Board for research involving covered entities.

#### **Federal Requirements for Single IRB Review**

- **NIH Requirements:**
  - Single IRB Review of multisite research **applies to** all studies that are:
    - Funded through grants, cooperative agreements, contracts, or the NIH Intramural Research Program, and
    - Involve non-exempt human subjects research, and

- Involve multiple sites, all of which are conducting the same protocol.
  - Single IRB Review of multisite research **does not apply to** studies that are:
    - Funded to foreign awardees and/or conducted at foreign sites, or
    - Funded through career development, research training or fellowship awards, or
    - Where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy, or
    - Collaborative projects in which multiple sites are involved but different sites may complete different parts of the study.
- **OHRP Requirements:**
  - Single IRB Review under 45 CFR 46.114(b) **applies to:**
    - All U.S. institutions engaged in cooperative research, and
    - The portion of the research conducted at domestic sites, and
    - Initially approved by an IRB on or after January 21, 2019
  - Single IRB Review of cooperative research **does not apply to:**
    - Cooperative research conducted or supported by HHS agencies other than the National Institutes of Health (NIH), if an IRB initially approved the research before January 20, 2020.
    - Cooperative research conducted or supported by NIH if either:
      - the NIH single IRB policy does not apply, and the research was initially approved by an IRB before January 20, 2020, or
      - NIH excepted the research from its single IRB policy before January 20, 2020.

### Process for Submitting Requests

The CRC IRB may enter into reliance agreements with other institutions for multisite or collaborative research in which investigators from BU CRC and the other institutions are engaged. The CRC IRB may serve as either the reviewing IRB or the relying IRB. Please note, however, the CRC IRB will not ordinarily provide oversight for large, multi-site clinical studies. CRC Investigators are encouraged to discuss their plan for oversight of the research with the CRC IRB before submitting grant proposals or reliance agreements to ensure appropriateness of the reliance plan.

To request the CRC IRB review or rely on another IRB, the following process should be followed:

- (1) To request that the CRC IRB serve as the reviewing or relying IRB, Investigators must submit the CRC [Single IRB Review Request Form](#), found on the IRB website, to the IRB Office.
- (2) In order for the CRC to be the reviewing or relying IRB, a Reliance Agreement must be set-up with the other participating institution(s) by one of the following methods:
  - [SMART IRB](#) is an online system that serves as both an IRB reliance agreement between reviewing and relying institutions, and system for investigators to request, track, and document study-specific reliance arrangements. The use of SMART IRB is required when both relying and reviewing institutions are signatories of this system.
  - If an institution is not a signatory of SMART IRB, an IRB Authorization Agreement may be used. The CRC IRB maintains a template that should be used, though this may be negotiated between the reviewing and relying IRBs. If the CRC template will not be used or if it will be modified, the CRC IRB Director must be notified.

#### Notes about Reliance Agreements:

- Documentation of reliance arrangements must be kept on file by both the reviewing and relying IRBs. The IRB is responsible for reviewing, facilitating, and maintaining IRB reliance agreements.
- The Institutional Official has designated the signing authority of reliance agreements to the IRB Director.

- The IRB will consult with the Institutional Official and/or General Counsel as necessary.
- (3) Once the Single IRB Application has been received by the CRC Office, the IRB Coordinator will log it in to the IRB tracking system, assign it a protocol number (if it does not have one already) and provide a copy of the application to the IRB Analyst and/or IRB Reliance Specialist.
- If the CRC is the reviewing IRB, the IRB Analyst will review the protocol per usual procedures, and the IRB Reliance Specialist will manage the reliance process with the CRC Investigator and the reviewing IRB.
  - If the CRC is the relying IRB, the IRB Reliance Specialist will manage the process with the CRC Investigator and the reviewing IRB.
  - The IRB Analyst and/or IRB Reliance Specialist will provide documentation to the CRC Investigator confirming the reviewing or relying status of the protocol, ordinarily within 5 days of the determination.

### **Reviewing and Relying Decisions**

The reviewing and relying IRBs ordinarily take the following factors into consideration when deciding whether to serve as the reviewing IRB or to rely on an external IRB:

- When research is greater than minimal risk, the reviewing IRB is accredited
- Requirements under federal policy
- Reviewing Institution selected by study sponsor
- IRB expertise
- Local context issues
- The participating institution has a process to review its investigator's financial conflicts of interest
- The IRB is registered and in good standing with OHRP
- Local and state laws
- Institutional policies
- Investigator and institutional resources
- Investigator qualifications
- Size and scope of the research

### **Institutional Responsibilities**

- **Management of Conflicts of Interest**

Each institution retains responsibility for managing the financial conflicts of interests (COI) of their Investigators and research personnel, including those responsible for the design, conduct and reporting of the research and communicating any such conflicts and management plans to the respective reviewing and relying IRBs. For example, if a reviewing IRB's Investigator has a management plan for a financial conflict of interest, the existence of the management plan will be disclosed to the relying IRB and relying site Investigator, and vice versa.

- **Ancillary or Institutional Reviews:**

Investigators at reviewing and relying institutions are responsible for obtaining and satisfying any additional ancillary or institutional reviews required by their respective institutions (e.g. radiation safety, pharmacy, COI, Privacy Board, EHS, etc.) and complying with all institutional requirements, regardless of which IRB reviews the research. Additionally, relying Investigators and Institutions/IRBs may be subject to additional requirements of reviewing Institutions/IRBs that they may not have to satisfy at their home institutions.

### **Investigator Responsibilities:**

- Investigators at relying institutions must comply with the policies and procedures of the reviewing IRB and with the approved protocol of the reviewing IRB, including any recruitment and consent procedures and documents, data collection procedures and materials, and compliance reporting.
- In the event of an audit or site visit (i.e. Sponsor, FDA, OHRP, relying or reviewing IRB quality

improvement or compliance personnel, accrediting agencies, etc.) allow the appropriate personnel from the relying or reviewing institutions access to research related records.

- Investigators at the reviewing and relying institutions must notify each other and the IRBs at their respective institutions of initial approvals or study closures, lapse in IRB approval, unanticipated problems involving risks to participants or others, serious or continuing non-compliance, suspension or termination of the research or study investigators, findings of misconduct, or FCOIs related to the research.

## 5.9 Privacy and Confidentiality in Research

Federal regulations require that, when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. As part of the IRB review process, the IRB will review the privacy and confidentiality provisions for each study to ensure that they are adequate for the study.

### Defined Terms

**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 that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

**Identifiable Private Information** is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

**Identifiable Biospecimen** is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

**Identifiable research materials** are identifiable to investigators who either have direct access to personally identifying information about subjects or codes, links or keys to identifying information.

**Coded** data/samples are not directly individually identifiable to the investigator but contain a code through which identifiers may be linked back to the specimen/data source by anyone who possesses the key to that code.

**Anonymized** data/samples are considered anonymized when the data/samples cannot be linked to a specific individual either (code or key) was never created or the link was destroyed.

**Confidentiality** refers to the researcher's agreement with the subject about how the subject's identifiable private information will be handled, managed, and disseminated.

**Directly Identifiable** data/samples are directly identifiable if they are labeled with unique identifiers that allow the identity of the subject to be ascertained or readily ascertained by the investigator or associated with the information.

**Indirectly Identifiable** data/samples that have a link (code or key) to identifiable information about the person.

**Non-identifiable** data/samples are considered to be non-identifiable when the data/samples cannot be linked to a specific individual either because the link (code or key) was never created or the link was destroyed.

### Privacy

Provisions for protecting the privacy of subjects should include a private location for the conduct of all study procedures including obtaining informed consent, limiting access to identifiable study information to those

with a need to have the information, and limiting the information being collected to only the minimum amount necessary to accomplish the study aims. The IRB will consider the following when reviewing the privacy provisions of a study:

- Purpose of the study
- Sensitivity of the information being collected
- Potential risk of harm of unintended disclosure of information
- Location and method(s) used for recruitment, consenting, and conducting study procedures
- Which members of the study team will interact with subjects
- Subject population

### **Confidentiality**

Investigators should be familiar with the BU data classification policy and the data protection standards for the type of data they are collecting and maintaining. The IRB will consider the sensitivity of the information being collected and the nature, probability and magnitude of harm that could occur as the result of unintended disclosure of study data. Provisions for maintaining confidentiality of subject data should be consistent with BU Information Security policies and procedures.

### **Notification of Privacy and Confidentiality for Subjects**

Subjects should be informed (ordinarily via the consent process and form) about how their privacy will be protected and how the confidentiality of their data will be maintained, for example:

- Who will know of their participation in the research
- How their data will be used
- How their data will be stored and the period for storage
- Whether their data will be stored with identifiers, or via codes and where they keys to codes will be kept and who will have access to that information
- Measures, systems, etc. to maintain the confidentiality of their data
- Any limitations of the confidentiality plan
- List of individuals/organizations outside of the research team who will have access to information (e.g. FDA, IRB, Sponsor, mandatory reporting, etc.).

### **Health Insurance Portability and Accountability Act (HIPAA) at BU**

If you are conducting research in a covered entity, you must comply with the HIPAA. The following components have been determined to be covered entities on the Boston University Charles River Campus:

- Sargent College Rehabilitation Services
- Physical Therapy Center at the Ryan Center for Sports Medicine and Rehabilitation Sargent Choice Nutrition Center
- The Danielsen Institute Boston University Health Plan

For more information regarding HIPAA at BU, please visit the [BU HIPAA webpage](#).

For more information on data security at BU, please visit the [BU Security for Researchers webpage](#).

## **5.10 Certificates of Confidentiality**

All biomedical, behavioral, clinical or other research that is funded by the NIH, and commenced or ongoing on or after December 13, 2016, and collects and/or uses identifiable sensitive information, is automatically covered under a Certificate of Confidentiality. Physical certificates are no longer issued. For the purposes of the NIH and PHS policy, the term ‘identifiable’ means that an individual is identified, and the term ‘sensitive information’ refers to a risk (including a very small risk) that a combination of the information, or a request for the information, and other available data could be used to identify or guess the identity of an individual.

Per NIH and PHS policy:



The recipient of a Certificate shall not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.

Disclosure is permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

Investigators conducting NIH supported research, per 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. As such, CRC Investigators should refer to the applicable policies on [the BU Security for Researchers webpage](#).

Investigators whose research is not funded or supported by the NIH may request and obtain from the NIH a Certificate of Confidentiality. Investigators who request and receive Certificates must follow the NIH and PHS policies governing such certifications.

## **5.11 International Research**

The CRC IRB requires that research with human subjects that takes place outside of the US complies with US regulations and guidelines and any applicable regulations and laws of the country in which the research is performed.

### **Principal Investigator Responsibilities**

When conducting international research, the Investigator is required to:

- Submit [Appendix A International Research Form](#), available on the IRB webpage, along with the IRB Application.
- Provide the same or equivalent protections to human subjects in research conducted in other countries
- Be aware of local laws, regulations, political and socio-economic factors, and cultural content
- Comply with local laws and adhere to cultural norms
- When applicable, provide documentation that the Investigator has permission to conduct research in the country. This documentation should be obtained from the appropriate local ethics committee, local experts, or community leaders. The OHRP [International Compilation of Human Research Protections](#) provides regulations, laws, and guidelines available per country.

### **IRB Review**

The IRB will review the research protocol to ensure that it includes the following information:

- The Investigators experience/qualifications for conducting research in this location with this community.

- If the research will be conducted in a language other than English, the Investigator must either state that they speak the language or, if they do not speak the language, describe the process for communicating with subjects
- The Investigators knowledge of local customs and culture; as appropriate, a local collaborator may be used/involved
- The payment method and schedule and how it relates to the local economy and subject income
- The consent process
- Plan for protecting the privacy of subjects and the confidentiality of the data
- Plan for communicating with the IRB for requesting amendments or reporting unanticipated problems, non-compliance and subject complaints
- Plans for post-approval monitoring. If applicable, the IRB may require review by the QI Specialist.
- Communication plan with local IRB's/ethics committees if appropriate

### **Risk Assessment**

When evaluating risk, different considerations may apply to research conducted outside of the US. Research that may be considered minimal risk in the US may be greater than minimal risk when conducted in other countries. The following will also be considered by the IRB:

- Questions that may be innocuous in the US may be offensive in other countries
- Assuring and maintaining confidentiality may be difficult in other countries
- Breach of confidentiality could have more dangerous consequences than in the US

The IRB may request consultation with individuals who are knowledgeable about the location and study population as necessary. The consultant may either be identified by the IRB or the IRB may request that the Investigator provide the name of an individual who is knowledgeable and can serve as a consultant. This individual does not need to be from Boston University.

### **Informed Consent**

The informed consent process should be conducted in the language most familiar to the subject and must consider local customs, literacy levels, and confidentiality concerns. The Investigator must be familiar with the cultural context regarding informed consent. This may differ from what is expected in the US. If the Investigator and/or study staff are not fluent in the local language, interpreters and/or translators who are fluent should be used for the study. Any documents that are translated into another language must be submitted to the IRB for review and approval prior to use. The Investigator must also submit an Attestation Form (available on the [IRB website](#)) with the translated documents.

The Investigator should request a waiver of documentation of consent if documentation of consent is not consistent with local customs. In some locations, documentation of consent may not be appropriate (e.g. subjects may not be literate, it may be inappropriate to ask for a signature, there may be legal or social implications when signing documents, or suspicion or fear when asked to sign a document, etc.).

### **Children**

The IRB will consider the following when research outside of the US involves children:

- The age an individual is legally considered an adult
- The relationship between parents and their children in the country
- Acceptable and effective parental permission processes
- If child assent it acceptable/permissible in that country

### **Student Research Projects**

Students who travel outside of the United States to conduct research must follow [BU Global Programs](#) policies, including review and approval of the Global Travel Risk Assessment Committee (GTRAC) for undergraduate travel to high risk destinations, as applicable.

## **Export Controls**

Due to potential export control concerns (depending on the country, research project, devices, equipment, technologies, research personnel country of origin, etc.), international research projects may be sent to the Export Control Office for review, prior to IRB approval.

## **5.12 ClinicalTrials.gov**

ClinicalTrials.gov is an online registry of clinical trials operated by the National Library of Medicine that captures key summary protocol information before and during the trial, as well as summary results and adverse event information of a completed trial. Clinical trial registration is required by the FDA, the NIH, and the International Committee of Medical Journal Editors (ICMJE). ClinicalTrials.gov provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. Boston University complies with the clinical trials registration and reporting requirements of the FDA, NIH and ICJME.

Investigators are responsible for ensuring compliance with clinical trials registration and reporting for their research. FDA, NIH and ICJME have differences in their definitions, as well as registration and reporting requirements. Please be sure to carefully review the below information to ensure that appropriate requirements are met for the research. In addition to the IRB office, there are several resources available to assist investigators in understanding their registration and reporting obligations.

### **FDA Requirements:**

The Food and Drug Administration Amendments Act (FDAAA) requires registration of “Applicable Clinical Trials” in ClinicalTrials.gov.

The FDAAA defines ‘Applicable Clinical Trial’ as:

- Interventional studies (drugs, biologics, devices);
- Phase 2 – 4 (excludes phase 1 drug studies, small feasibility device studies, observational studies, single patient expanded access studies);
- US FDA jurisdiction (e.g., IND/IDE or U.S. site);
- Studies initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007.

Timeline for Registration, Updates and Results Reporting in ClinicalTrials.gov:

- Registration must occur within 21 days of enrollment of 1st subject;
- Updates must be submitted at least every 12 months (30 days for Recruitment Status and Primary Completion Date);
- Reporting of summary results must be submitted no later than one year after the completion date, regardless of whether the product (drug, biologic, device) has been approved, licensed, or cleared by the FDA. Primary completion date is the date that the final participant was examined or received an intervention for the purpose of collecting the data for the primary outcome measure.

Responsible Party:

- For Applicable Clinical Trials when there is an IND or IDE, the IND/IDE holder is generally considered to be the sponsor and responsible for registration, unless that responsibility has been designated to a Principal Investigator;
- For Applicable Clinical Trials when there is no IND or IDE, the institution that received the funding award is generally considered to be the ‘sponsor’ and responsible for registration. At CRC, the Principal Investigator will ordinarily be considered the ‘responsible party’ for registering their trial and meeting clinicaltrials.gov submission requirements.

#### Consent Form Requirements:

- If the study will be registered on [clinicaltrials.gov](http://www.clinicaltrials.gov), the following statement must be included in the consent form: “A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”
- For each clinical trial conducted or supported by Federal department or agency, one IRB-approved consent form used to enroll subjects must be posted by the principal investigator on a publicly available Federal website such as [clinicaltrials.gov](http://www.clinicaltrials.gov). The informed consent form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

For more information on the FDA registration and results reporting, please refer to:

- <https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11>
- <https://classic.clinicaltrials.gov/ct2/manage-recs/fdaaa>

#### **NIH Requirements:**

The NIH policy requires registration of **all clinical trials** funded in whole, or in part, by the NIH, in [clinicaltrials.gov](http://www.clinicaltrials.gov). The NIH requirements go farther than those of the FDA and include NIH-funded Phase I drug studies and clinical trials of social-behavioral interventions.

The NIH defines clinical trials as:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Timeline for Registration, Updates and Results Reporting in [ClinicalTrials.gov](http://www.ClinicalTrials.gov):

- Registration must occur within 21 days of enrollment of 1st subject;
- Updates must be submitted at least every 12 months (30 days for Recruitment Status and Primary Completion Date);
- Reporting of summary results must be submitted no later than 12 months after the completion date. Primary completion date is the date that the final participant was examined or received an intervention for the purpose of collecting the data for the primary outcome measure.

Responsible Party:

The institution that received the funding award is generally considered to be the ‘sponsor’ and responsible for compliance with NIH policies, including [clinicaltrials.gov](http://www.clinicaltrials.gov) registration, updates and results reporting. At CRC, the Principal Investigator listed on the funding application and responsible for overseeing the trial will ordinarily be the responsible party for registering their trial and meeting [clinicaltrials.gov](http://www.clinicaltrials.gov) submission requirements.

Consent Form Requirements:

- If the study will be registered on [clinicaltrials.gov](http://www.clinicaltrials.gov), the following statement must be included in the consent form: “A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”
- For each clinical trial conducted or supported by Federal department or agency, one IRB-approved consent form used to enroll subjects must be posted by the principal investigator on a publicly available Federal website such as [clinicaltrials.gov](http://www.clinicaltrials.gov). The informed consent form must be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

For more information on the NIH requirements for clinical trial registration and results reporting, please refer to: <https://grants.nih.gov/policy/clinical-trials/reporting/index.htm>.

### **ICJME Requirements**

The International Committee of Medical Journal Editors (ICMJE) requires clinical trial registration as a ‘condition of consideration’ for publication. The ICMJE accepts registration in any registry that is a primary register of the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

The ICMJE defines a clinical trial as:

Any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention *and* a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioural treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

Timeline for Registration, Updates and Results Reporting:

- Registration should occur before the first person consents to participate in the research.
- Authors should include a statement that indicates when the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.
- The ICMJE does not require registration of observational studies or studies involving secondary data analyses of primary (parent) clinical trials, but ICJME notes that these types of studies should reference the registration number of the primary trial(s). The ICJME further recommends that, when in doubt of whether registering is required, that Investigators err on the side of registering their trial.
- The ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies but does not require results reporting for registered trials.
- The ICMJE accepts registration in the numerous online registries, including ClinicalTrials.gov.

Responsible Party:

The sponsor (or designee) of the clinical trial is responsible for meeting the registration requirements. For more information regarding ICMJE requirements, please refer to the ICMJE website.

For more information on the ICJME requirements for registration and results reporting, please refer to: <https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>.

### **CRC IRB Requirements:**

At the time of the IRB submission, the investigator must determine and document in the IRB Application if their study meets the requirements for registration in accordance with FDAAA, NIH and ICJME policies. If registration is required, the investigator must provide the National Clinical Trial (NCT) Identifier number received at the time of registration to the IRB; the study cannot be approved by the IRB until the NCT number is confirmed.

Investigators are required to comply with clinical trials registration and results reporting. If an investigator fails to comply with this policy, the IRB Director or their designee will notify the applicable Department chair, Research Dean, and other institutional officials as applicable. Failure to comply will result in notification to the IRB noting regulatory noncompliance in research registration and/or results reporting.

## Transfer of Responsible Party Responsibilities

If the principal investigator (PI) leaves BU during the course of the clinical trial and the PI is the Responsible Party (RP), the PI is responsible for working with their Department Chair and the CRC IRB to ensure that the RP responsibilities are transferred to a new BU PI or the that the ClinicalTrials.gov account and RP responsibilities are transferred to the departing PI's new institution. If a PI leaves BU without transferring PR responsibilities, the Department Chair is responsible for assuming the PR obligations or appointing another PI to serve as the RP who will assume the RP responsibilities.

### Summary Table:

Regulation / Policy	Timeline for Registration	Timeline for Results Reporting	Enforcement
Food and Drug Administration Amendments Act (FDAAA) 801	21 days after enrollment of first subject	No later than 12 months after completion date	<ul style="list-style-type: none"> <li>• Initial \$10,000 <i>and</i></li> <li>• \$10,000/day for duration of violation (uncorrected)</li> <li>• Withholding of funds</li> <li>• Sanctions</li> </ul>
International Committee of Medical Journal Editors (ICMJE)	At or before enrollment of first subject	No specific timeline	<ul style="list-style-type: none"> <li>• Refusal to publish</li> </ul>
National Institutes of Health (NIH)	21 days after enrollment of first subject	No later than 12 months after the completion date	<ul style="list-style-type: none"> <li>• Withdrawal of funding</li> <li>• Suspending or terminating current award</li> <li>• Withholding future award</li> </ul>

## 6 Continuing Review of Research

The CRC IRB conducts continuing review of research requiring review by the convened IRB in accordance with 45 CFR 46.109(e) and 21 CFR 56.109(f), at intervals appropriate to the degree of risk, but not less than once per year.

Unless the IRB determines otherwise, continuing review of research is *not* required in the following circumstances [45 CFR 46.109(f)]:

- (i) Research eligible for expedited review in accordance with [§ 46.110](#);
- (ii) Research reviewed by the IRB in accordance with the limited IRB review described in [§ 46.104\(d\)\(2\)\(iii\)](#), [\(d\)\(3\)\(i\)\(C\)](#);
- (iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
  - (A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
  - (B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

The investigator will be required to provide an annual update to the IRB for expedited research that does not require continuing review by the convened IRB.

The IRB may determine that continuing review *is* required for research that falls within 45 CFR 46.109(f), above, and if so, will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter. Instances in which the IRB may determine that continuing review is still required include:

- The research involves topics, procedures, or data that may be considered sensitive or controversial;
- The research involves vulnerable populations;
- The investigator has minimal experience in research or in the research topic;
- The investigator has a history of non-compliance.

### Continuing Review Procedures:

Investigators should submit the following materials for review, as applicable to their research:

- Continuing Review and Annual Update Form
- Informed consent forms, assent forms and information sheets
- Recruitment and screening materials
- Data collection instruments (e.g., questionnaires, surveys, assessments, etc.)
- Sponsor/NIH Progress reports
- DSMB/Monitoring Reports
- List of data collection materials (e.g., questionnaires, surveys, assessments, etc.)

The Continuing Review/Annual Update Application includes a summary since the last IRB review of:

- Adverse events and adverse outcomes experienced by subjects;
- Unanticipated problems involving risks to subjects or others;
- Subject withdrawals (voluntary or by PI) and the reasons for withdrawals;
- Subject complaints about the research;
- Significant changes to the research or research materials;
- Any relevant recent literature, interim findings and/or multi-center trial and DSMB reports;
- Study progress and current status, including enrollment. If the study is still open to enrollment, the IRB Reviewer will confirm that:
  - The current consent document is still accurate and complete;
  - Any significant new findings are communicated to subjects who have already enrolled.

Once materials are received by the IRB Office, the IRB Coordinator conducts administrative pre-reviews to check for missing or incomplete documents and for training requirements. Incomplete submissions are

returned to the Principal Investigator (PI) or held by the Coordinator until the submission is complete. The IRB Coordinator enters the continuing review/annual update submission into the IRB tracking system and assigns the Application to the appropriate IRB Analyst for review. If the continuing review will be reviewed by expedited procedures the IRB Analyst (in their capacity as an IRB member) will serve as the IRB Reviewer. If the continuing review will be reviewed at a convened meeting, one of the regular IRB members will be assigned by the Analyst or Director as the Primary Reviewer. The IRB must determine that the regulatory criteria for approval (45 CFR 46.111 and 21 CFR 56.111) are met, as outlined in 4.9. The IRB Reviewer and/or IRB Analyst will complete the appropriate Reviewer Worksheets and Approval Checklists as part of the approval process.

### **Continuing Approval Dates**

The CRC IRB maintains fixed approval dates, as long as the research is reapproved within 30 days prior to expiration. If the approval expires, the date of approval will change to the date the protocol is fully reapproved, and subsequent continuing review anniversary dates will be the date of approval, and the date of expiration will be the date the following year, minus one day, unless the IRB determines that more frequent continuing review is necessary.

### **Lapse in Continuing Approval**

The IRB Coordinator sends courtesy reminders via email to PIs and designated contacts approximately six weeks and two weeks prior to the IRB expiration date. Once the study expires, the Coordinator will send an e-mail to the PI confirming that the study is expired and that all research activities must stop. The expiration date is the last date that the protocol is approved.

When IRB approval has expired, continued participation of already enrolled subjects may occur if:

- There is an over-riding safety concern or ethical issue such that the best interests of individual subjects are served by allowing these subjects to continue to participate in the research;
- There is the prospect of direct benefit to the subjects;
- Withholding research interventions poses an increase risk to subjects.

If the Principal Investigator believes that it is in the best interest of already enrolled subjects to continue participation, they should submit a request to the IRB Director and/or IRB Chair. The request should include the rationale for allowing continued participation of the subjects. The request will be reviewed by the IRB Director and/or IRB Chair, and others (including) consultants, as necessary. Enrollment of new subjects into a study where IRB approval has expired is not allowed.

If the Principal Investigator does not submit the Continuing Review/Annual Update Application within 30 days of the protocol expiration date, the IRB may suspend or terminate the protocol. The IRB will notify the PI of suspension/termination decisions. The PI may appeal any suspension/termination decisions. Once a protocol is terminated, the PI may be required to submit a New IRB Application if they wish to continue their research.

### **Investigator Notification:**

IRB staff will communicate the determination in writing (as well as the rationale for the decision) to Investigators within 5 days of review.

## **6.1 Research Requiring Verification from Sources other than Investigators that no Material Changes have occurred since the last IRB Review**

In some circumstances (e.g. when there is suspected non-compliance with IRB determinations, when the materials submitted to the IRB are inconsistent with previously submitted or approved materials, when the Investigator has a history of non-compliance), the IRB may request verification from others such as a Department Chair, Project Director, or a research monitor that no material changes have occurred since the prior CRC IRB review and approval, per 45CFR46.108(a)(3)(ii), or, in the case of a conditional approval at



Continuing Review, verification by an independent source that all of the IRB's requested changes have occurred.

## **6.2 Study Closure**

In addition to the failure to submit a Continuing Review Application within one month following expiration, a research project may be closed when it no longer involves human subjects. A research project no longer involves human subjects once the Investigators have finished obtaining data through interaction or intervention with subjects or obtaining or using identifiable data about, or biospecimens from, the subjects.

Study closure may also be appropriate if the jurisdiction of IRB review has been transferred to another institution. Transfer of jurisdiction occurs when an Investigator leaves BU for another institution and will be conducting their research at that institution, or when their grant is administered through or transferred to another institution and no research activities are (or are no longer) taking place at BU.

To close a study, Investigators must submit a Study Closure Form. The IRB Office will send confirmation to the PI of the study closure.

## 7 Modifications to Approved Research

Federal regulations at 45 CFR § 46.108(a)(3)(ii & iii) and [21 CFR § 56.108\(a\)\(4\)](#) require IRBs to review proposed changes in research activity and to ensure that such changes are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to research participants. This policy applies to research reviewed by the convened IRB, expedited procedures and exempt research. In reviewing amendments, the IRB/reviewer must determine that the regulatory criteria for approval (45 CFR 46.111 and 21 CFR 56.111) are still met, and whether already-enrolled subjects need to be informed about the changes included in the amendment and whether they should be re-consented.

Investigators making changes to approved research must submit the Amendment Form and all applicable documents that are to be revised or added to the CRC IRB for review (e.g., consent/assent/information sheet, recruitment/screening materials, questionnaires/surveys/data collection materials, updated IRB applications, etc.). Personnel changes are made using the Study Staff Amendment form.

### **Amendment Review Process**

Once materials are received by the IRB Office, the IRB Coordinator conducts administrative pre-reviews to check for missing or incomplete documents and for training requirements. Incomplete submissions are returned to the Principal Investigator (PI) or held by the Coordinator until the submission is complete. The IRB Coordinator enters the submission into the IRB tracking system and assigns the Application to the appropriate IRB Analyst for review. If the amendment will be reviewed by expedited procedures the IRB Analyst (in their capacity as an IRB member) will serve as the IRB Reviewer. If the amendment will be reviewed at a convened meeting, one of the primary IRB members will be assigned by the Analyst or Director as the Primary Reviewer.

### **Amendments Reviewed by Expedited Procedures**

Minor changes in previously approved research can be reviewed using expedited procedures. Minor changes are those that do not: 1) alter the risk to benefit assessment for the participants, 2) affect the safety of the subjects, 3) add new medical, social, or psychological risks, 4) significantly alter the design or scientific aims of the study, or 5) affect a subject's willingness to continue participation in the study. Examples include minor wording or formatting changes to consent forms, recruitment materials, or interviews, minor increase in enrollment number, adding a study visit or procedure that does not alter the risks, change to the eligibility criteria if it does not affect the risk/benefit assessment, addition/removal of study staff.

### **Amendments Reviewed by the Convened IRB**

Amendments that are determined to involve more than a minor change will be reviewed at a convened meeting. Changes that are more than minor are those that: (1) alter the risk-to-benefit assessment, (2) affect the safety of the subjects, (3) add new medical, social, or psychological risks, (4) significantly alter the design or scientific aims of the study, (5) affect a subject's willingness to continue participation in the study. Examples include the addition of a vulnerable population, information about new risks, removal of safety evaluations, any change determined by the IRB to involve more than a minor change.

### **Changes to Exempt Research**

Changes to exempt research are submitted to the IRB using the [Clarification Form](#) and are only needed when limited IRB review was used to approve the research, when the change affects the provisions to protect the privacy of the subjects and to maintain confidentiality of the data, when there is a change to the PI, and when the change may alter the criteria so that the research no longer qualifies for an exemption. If, during the review, the IRB determines that the proposed change alters the criteria so that the research no longer meets exemption criteria, the IRB will contact the Investigator. If the Investigator wishes to proceed with the change, the IRB may require that the Investigator submit a new IRB Application. Investigators with questions about whether a change to exempt research requires review should contact the IRB Office.

**Changes to Eliminate Immediate Hazards**

If an Investigator needs to make a change to eliminate an immediate hazard, this must be reported to the IRB within 5 days. The IRB will review these changes: 1) as possible unanticipated problems involving risks to subjects and others and 2) to determine if the change is consistent with ensuring the subjects' continued welfare.

**Investigator Notification**

IRB staff will communicate the review determination, ordinarily within 5 business days, in writing to the PI. Approval dates for modifications do not ordinarily alter the date of the annual renewal or check-in.

## 8 Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

In the course of a research project various problems and events can arise, some of which may affect or increase the risk to the research participants. Some of these problems/events may be related to the research, and some may be unrelated to the research. Some may be expected, and some may be unexpected. This policy section describes which events need to be reported to the IRB (and if necessary to other offices and authorities), the timing and information required for reporting, and the IRB review of such events.

**Defined Terms** (all definitions are those of DHHS, unless otherwise specified)

**Adverse event:** 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. Adverse events encompass both physical and psychological harms. (In FDA regulated studies, the term "adverse event" is generally understood to mean any untoward medical occurrence associated with the use of an FDA regulated product. More specific drug and device definitions are addressed below.)

**External adverse event:** From the perspective of one particular institution engaged in a multicenter clinical trial, external adverse events are those adverse events experienced by subjects enrolled by Investigators at other institutions engaged in the clinical trial.

**Internal adverse event:** From the perspective one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by the Investigator(s) at the BU CRC site. In the context of a single-center clinical trial, all adverse events would be considered internal adverse events (e.g. CRC sites, sites covered under the CRC IRB review, sites with a CRC PI).

**Possibly related to the research:** There is a reasonable possibility that the adverse event, incident, experience or outcome may have been at least partially caused by the procedures involved in the research.

**Serious adverse event:** Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity (under the FDA drug regulations this includes "or the substantial disruption of the ability to conduct normal life functions");
- results in a congenital anomaly/birth defect;
- or any other adverse event that, 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).

**Unanticipated problem involving risks to subjects or others:** Any incident, experience, or outcome that meets **all** of the following criteria:

1. 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;
2. related or possibly related to a subject's participation in the research (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

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

**Unexpected adverse event:** Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is *not* consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in
  - (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable Investigator brochure, and the current IRB-approved informed consent document, and
  - (b) other relevant sources of information, such as product labeling and package inserts; or
2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

**Unanticipated Adverse Device Effect as defined by FDA:** any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Unexpected Adverse Drug Experience as defined by FDA:** Any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator brochure; or, if an Investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g. included in the Investigators brochure) rather than the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

### **8.1 Reporting Requirements to the IRB**

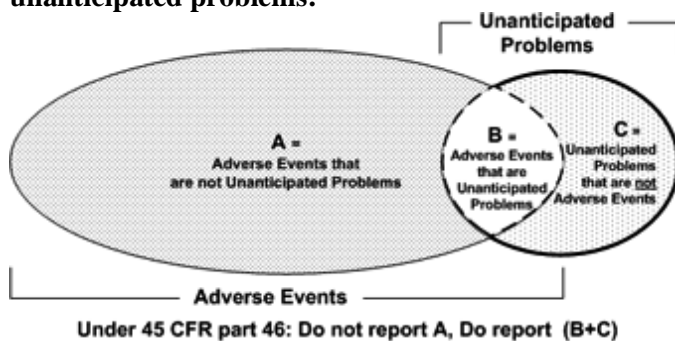
Investigators must report to the IRB any unanticipated problems involving risks to subjects or others (see definitions above, and figures 1.1 and 1.2 below) using the Event Form. Unanticipated problems (including unanticipated adverse events) that are related or possibly related to the research must be reported within 5 working days of discovery. Investigators must submit unanticipated problems (and adverse events, if so required) to the sponsor and other applicable agencies as appropriate; any necessary reporting to Federal oversight bodies will be handled by the IRB Office.

Incidents requiring reporting to the IRB include:

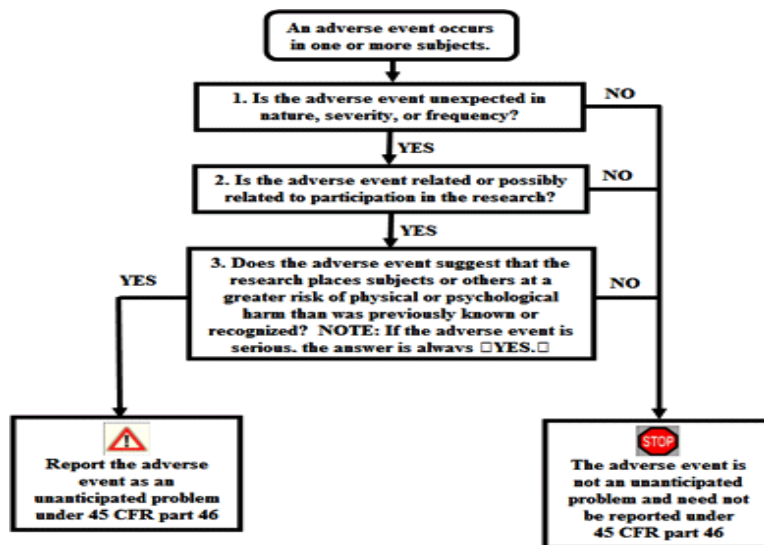
- Death of a research subject if the death is related or possibly related to the research study
- Any event or problem, including an adverse event, that is unanticipated in terms of nature, severity, or frequency, related or possibly related, and suggest that there is an increased risk to subjects or others than was previously known
- Breach of privacy or confidentiality
- Suspension or termination of the research study by the Sponsor, oversight agency, institutional official, reviewing IRB, or other oversight body
- Unexpected incarceration of a research subject
- Study staff misconduct
- Medication or laboratory error regardless of whether subjects experienced harm
- New information (e.g. interim analysis, safety monitoring report, publication, or other finding) that suggests there are new or increased risks to subject or others
- A complaint by a research subject or others that suggests that rights, welfare, or safety of a subject has been adversely affected
- Any other problem that suggests that the research places subjects or others at an increased risk for harm

or adversely affects the rights, welfare or safety of subjects or others

**Figure 1.1** Venn diagram summarizing the general relationship between adverse events and unanticipated problems:



**Figure 1.2** Algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under regulations at 45 CFR part 46.



Note: An unanticipated problem involving risks to subjects or others may exist even when actual harm does not occur to any participant. Therefore, although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include (i) improperly staging a participant’s tumor resulting in the participant being assigned to an incorrect arm of the research study; (ii) the theft of a research computer containing confidential subject information; and (iii) the contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/form or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

## 8.2 IRB Review of Reported Events

The Principal Investigator (PI) is responsible for submitting unanticipated problems using the Event Form to the IRB Office. When received, the IRB Coordinator will screen the submitted material for completeness. If information is missing, the IRB Coordinator will request the missing information from the PI. The IRB Coordinator forwards the Event Form to the IRB Analyst for review. If necessary, the Analyst will send the Event Form and related materials to an additional IRB reviewer (e.g., a subject matter expert). Once a

preliminary determination of whether the event is an unanticipated problem (or not) is made, the Analyst will forward the relevant information/materials and determination to the IRB Director for concurrence.

- If the IRB Director concurs that an event does not meet criteria for an unanticipated problem, the IRB Analyst will send an acknowledgement of the event and any additional recommendations to the PI.
- If the IRB Director concurs that an event meets criteria (or if it is unclear) for an unanticipated problem involving risks to subjects or others, the event will be forwarded to the IRB Chair/Vice Chair for further review.

The IRB Chair/Vice-Chair will review the event to determine whether it (1) is unexpected; (2) is related or possibly related to the research, and (3) indicates that participants or others are at increased risk of harm. If all criteria are met, the event is considered to be an unanticipated problem involving risks to participants or others and requires review by the convened IRB.

- If the event *does not* meet the definition of an unanticipated problem involving risks to subjects or others, the IRB Chair/Vice-Chair and IRB Director will conduct the review using expedited procedures.
- If the event *does* meet the definition of an unanticipated problem involving risks to subjects or others, it will be referred to the full board for review.
- If a determination is unable to be made, including after discussion with the PI and others as necessary, the event will be referred to the full board for review.
- If additional expertise is needed, the IRB Director will contact the appropriate consultant for review.

The reviewers will use the appropriate checklist for their determinations, as well as any corrective action plans needed by the Investigator. Expedited review of determinations will be reported at the next convened meeting.

The assigned reviewer and all IRB members attending the meeting will receive the following materials as applicable:

- Event Form
- Correspondence regarding the event
- IRB Application
- Informed Consent Form
- Event Reviewer Checklist
- Other materials related to the event and/or to the investigation of the event
- The full board will review the event, determine if the event meets the definition of an unanticipated problem involving risks to others, and determine the appropriate corrective action.

Corrective actions for the PI and research team may include:

- Education for the PI and research team
- Modifications to the protocol, consent form or other study materials or procedures
- Notification of current and/or past subjects, including possible reconsenting of subjects
- More frequent IRB review
- Additional quality improvement monitoring
- Prohibit use of study data
- Suspend enrollment of new participants, or suspend some or all of the study procedures and/or data analysis;
- Terminate the study approval;
- Refer the matter to other institutional offices or committees as appropriate.

If the event is determined to be an unanticipated problem involving risks to subjects and others, it will be reported as outlined in the Reporting section of this policy manual. The IRB will also determine if the event meets the definition of serious and/or continuing non-compliance; if so, it will be processed as outlined in the Noncompliance section of this policy manual. The PI will be notified of the determination and any correction action plan ordinarily within 5 business days of the final determination. However,

- If the IRB determines that a study needs to be suspended or terminated immediately, the Investigator will be notified by phone or email immediately after the meeting.
- In cases where enrollment in the study had been temporarily halted and the halt has been lifted, the Investigator will be notified immediately after the meeting by phone or email.

**Additional Requirements for studies subject to FDA Regulations:**

- Investigational Devices (IDE): A sponsor who conducts an evaluation of an unanticipated adverse device effect under 21 CFR 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect.
- Bioequivalence/Bioavailability: When conducting bioequivalence or bioavailability studies, the person conducting the study must notify FDA and all participating investigators of any serious adverse event, as defined in 21 CFR 312.32(a), observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence.
- Investigational New Drugs (IND): The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

**Subject Complaints and Unanticipated Problems**

Subject complaints that are not submitted to the IRB using an Event form are reported/forwarded to the IRB Director. The IRB Director will investigate the complaint including contacting the subject as appropriate. The complaint will then be handled in accordance with the process described above. If it is determined to be an unanticipated problem involving risks to subjects or others, the procedures in this Section will be followed. Subject complaints that are not unanticipated problems are addressed in the Community Engagement and Information for Research Participants and Family Members section of this policy manual.

**8.3 Data Safety Monitoring Boards/Safety Monitoring Committees and External Events**

Data Safety Monitoring Boards (DSMBs) and Committees (DSMC, or SMCs) may be required by the IRB or the study sponsor for interventional clinical trials and multi-site clinical trials. A DSMB/C is ordinarily relied upon to determine safety and effectiveness of a trial and to recommend the closure of a trial when significant risks or benefits have developed or when a trial is unlikely to be successful.

Studies engaging a DSMB/C should submit the data safety monitoring plan (also referred to as a DSMP) for IRB review and approval. The monitoring provisions should be tailored to the expected risks of the research; the type of subject population being studied; and the nature, size (in terms of projected subject enrollment and the number of institutions enrolling subjects), and complexity of the research protocol. Sponsors may have specific requirements for DSMPs, but in general, safety plans should include one or more of the following elements:

- The type of data or events that are to be captured under the monitoring provisions;
- The entity responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the Investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB/DMC, some other entity);
- The time frames for reporting adverse events and unanticipated problems to the monitoring entity;
- The frequency of assessments of data or events captured by the monitoring provisions;
- Definition of specific triggers or stopping rules that will dictate when some action is required;
- As appropriate, procedures for communicating to the IRB(s), the study sponsor, the Investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.



## **8.4 Reporting Requirements to Authorities**

Federal regulations at 45 CFR § 46.108(a)(4)(i) and 21 CFR § 56.108(b)(1), require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head sponsoring the research of any unanticipated problems involving risks to research participants or others, any serious or continuing noncompliance with federal regulations or the requirements or determinations of the BU IRB, or suspension or termination of IRB approved research.

The IRB Director and the IRB Chair are responsible for preparing event reports. The report will include the following information:

- Name of the institution
- Title of the research project and CRC IRB protocol number
- Grant/award number
- Name of the Principal Investigator
- Summary of the study
- Summary of the event
- Description and findings of an investigation, if one occurred
- Determination(s) of the IRB
- Actions the institution is taking or plans to take to address the problem

The completed event report will be sent by the Director to following individuals, as applicable:

- Institutional Official
- IRB Chair (and IRB members, if appropriate)
- OHRP (if federally funded)
- Department Chair
- School Dean
- Principal Investigator
- Faculty Advisor
- Sponsor of the research
- Food and Drug Administration (FDA), if the study is subject to FDA regulations
- Federal Agency supporting or overseeing the research
- Others, as deemed appropriated by the Director, Chair and IO

The IRB Director and Chair will ensure that the procedures in this policy are completed ordinarily within 30 days of the date when:

- The IRB determines that the event is an unanticipated problem involving risks to subjects or others
- The IRB determines that the event is serious or continuing noncompliance
- The IRB or IO suspends or terminates IRB-approved research

The CRC's FederalWide Assurance is limited to federally funded research. The same criteria and process for conducting noncompliance investigations, making determinations about reporting, and actions will apply to all research regardless of funding source. If an event that would otherwise require reporting to regulatory agencies involves research that is not federally funded, the event will be reported to the PI's Department Chair/Dean (as appropriate), Institutional Official, and other federal agencies as required under the sponsorship agreement. Depending on the nature or the severity of the non-compliance, the IRB reserves the right to voluntarily report to the Office for Human Research Protections (OHRP) any event that is not federally funded.

### **Reporting to AAHRPP:**

The IRB Director will report to AAHRPP, its accrediting agency, within 48 hours of becoming aware of any of the following:

- Any negative actions taken by a government oversight office, including, but not limited to, OHRP compliance oversight determination letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, or FDA restrictions placed on the CRC IRB or its Investigators.
- Any litigation, arbitration, or settlements initiated related to human research protections.
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding the CRC HRPP.

## 9. Protocol Deviations and Issues of Non-compliance

The purpose of this section is to define the responsibility of individuals to report to the IRB any observed or suspected non-compliance with federal, state and local laws and regulations or with the requirements of the IRB, and to describe the procedures the IRB follows when reviewing reports of potential non-compliance. Non-compliance with an IRB approved protocol is sometimes also referred to as a Protocol Deviation. For the purposes of this policy, protocol deviations are a sub-category of non-compliance, and are reviewed in accordance with this policy.

### Defined Terms:

**Protocol Deviation:** any departure in the research activity from the current IRB-approved protocol and approved study materials. Protocol deviations are non-compliance with the IRB-approved protocol or approved study materials.

**Non-Compliance:** failure to comply with the regulations, accepted ethical guidelines, the IRB policies and requirements, and/or determinations of the IRB, including the IRB-approved protocol or approved study materials.

**Minor Non-Compliance:** A non-compliant event that does not 1) adversely affect the rights and welfare of the subjects, 2) increase risks to subjects or impact their safety, 3) compromise the integrity of study or validity of the data. Examples include:

- Over-enrollment of study subjects
- Use of an expired consent form that includes all the required information and elements of informed consent
- Informed consent documentation errors (e.g. missing signatures or dates, copy not given to subject, etc.)
- Study visits/procedures that are either omitted, conducted outside of the visit window or in a different order than specified in the protocol, and/or that do not affect or have the potential to affect subject safety or data integrity
- Lapse in continuing IRB approval of research due to missed deadlines where no research is conducted during the period of lapse
- Minor edits to study materials
- Failure to obtain a determination of exemption or non-human subjects research from the IRB before such research is conducted.

**Serious Non-Compliance:** Non-compliance that 1) adversely affects or that jeopardizes the rights and welfare of participants, 2) places participants at increased risk of harm, or 3) jeopardizes the integrity of the study and validity of study data. Examples of serious non-compliance include:

- Failure to obtain informed consent or assent
- Obtaining informed consent after study procedures have been initiated
- Performing study procedures that have not been approved by the IRB and may adversely affect the rights, welfare and/or safety of subjects
- Enrolling a prisoner into the study if the study is not approved to enroll prisoners
- Failure to report serious adverse events and unanticipated problems to the IRB, Sponsor, and other agencies as outlined in the study protocol and IRB policies and procedures
- Enrollment of a subject who did not meet the inclusion/exclusion criteria if enrollment adversely affects the rights, safety and/or welfare of those subjects.

**Continuing Non-Compliance:** Non-compliance that occurs in a persistent and repeated manner that indicates a pattern of an unwillingness to comply with the regulations, accepted ethical guidelines, the IRB policies and requirements, and/or determinations of the IRB or a lack of knowledge that may lead to an adverse effect on the rights and welfare of participants, place participants at an increased risk of harm, or jeopardize the

integrity of the study and validity of the data. Examples of continuing non-compliance include:

- Repeated instances of allowing a study (or multiple studies) to expire before it/they is/are re-approved;
- Repeated failure to respond to IRB inquiries or requests for documentation;
- Repeated failure to respond to and resolve any study conditions; or
- Other instances of repeated minor non-compliance, each of which standing alone would not necessarily be serious but are part of a pattern of disregard for applicable requirements and suggest a sub-standard approach to the conduct of research.

### **Investigator Reporting Requirements**

Investigators are required to report incidents of noncompliance and other events that are not consistent with the IRB approved protocol by telephone or email as soon as possible but no later than within 5 business days of learning of serious non-compliance, and within 20 business days of learning of minor non-compliance; if Investigators have reported by phone or email, they are required to submit an Event Form within 5 business days of that reporting, unless otherwise specified by the IRB office.

Investigators or their study staff designee ordinarily report deviations and non-compliance however, there are times when allegations of non-compliance are reported by those either within the research team, or outside of the research team, including by study participants. Allegations of non-compliance may be submitted directly to the IRB office, the Institutional Official, or via the BU Ethics and Compliance Hotline. Noncompliance may also be discovered during an internal (e.g., QI review) or external (e.g., sponsor, FDA, etc.) audit. All allegations or discoveries of non-compliance (including those that are anonymous) will be investigated promptly.

### **IRB Review Process**

The IRB is responsible for investigating allegations of noncompliance, determining appropriate actions for any findings of noncompliance, and reporting any findings of serious and/or continuing noncompliance to the appropriate institutional officials, regulatory agencies and sponsors.

Upon receipt of an Event Report, the IRB Coordinator will provide the report to the IRB Analyst responsible for reviewing the protocol. The Analyst will review the report and related materials and make an initial determination of whether the non-compliance is minor, serious and/or continuing, or if more information is needed, and will provide the Event Report along with their determination and reviewer sheet to the IRB Director for concurrence. The IRB Assistant Director will consult with the IRB Chair if there is uncertainty regarding whether an Event may be minor or serious and/or continuing, and whether the event may be reviewed by expedited procedures, or if it should be reviewed by the convened IRB.

If the non-compliance is minor, the IRB Analyst will forward this determination and any corrective actions to the Investigator. Events reviewed by Expedited procedures will be reported to the IRB at the next convened meeting.

If the facts support a finding of serious and/or continuing noncompliance, the event will ordinarily be referred to the convened IRB for review. The assigned reviewer and all IRB members attending the meeting will receive the following materials as applicable:

- Event Form
- Correspondence regarding the event IRB Application or Informed Consent Form
- Event Reviewer Checklist
- Other materials related to the event and/or to the investigation of the event

The actions that the convened IRB may take include, but are not limited to:

- Dismissal of the allegation
- Determination of minor noncompliance
- Determination of serious and/or continuing noncompliance

- Require more information in order to make a determination
- Imposition of remedial education for the Investigator and/or other personnel working on the study
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to past participants
- Notification to current participants when information might relate to their willingness to continue to take part in the research
- Requiring re-consent of current participants
- Modification of the continuing review schedule
- Additional monitoring of the research
- Monitoring of the consent process
- Restrictions on research practice, such as limiting the Investigator to conducting studies with only minimal risk or conducting research under supervision
- Suspension of approval for one or more of the Investigator's studies
- Termination of approval for one or more of the Investigator's studies
- Referral to other BU officials or committees for further review and/or action, which may include the suspension or termination of the Investigator's research privileges at BU.

At any time during the IRB review process, the Investigator may request a meeting with the IRB staff, Chair, or request time to discuss the issue at a convened IRB meeting. The written report of the findings and IRB determinations will be sent to the Principal Investigator and any other individuals involved as appropriate. If the event is determined to be serious and/or continuing noncompliance it will be reported as outlined in the "Reporting Policy." Regardless of the type of review the Event receives, the IRB Analyst will communicate the determination to the PI via letter within 5 business days.

#### **Coordination with Other Investigative Processes**

As appropriate, the IRB will cooperate with other BU offices or committees, or with federal agencies such as OHRP or the FDA, which may be conducting an inquiry, investigation, review or audit involving an Investigator or research study about whom or which the IRB has knowledge or documentation. Upon receipt of notification of an investigation by federal agencies, the Institutional Official, General Counsel and IRB Chair/Vice Chair will be notified, as appropriate.

Where the IRB and another BU committee are conducting concurrent inquiries, investigations, reviews or audits involving the same or related allegations, the IRB will work to coordinate with the other committee(s) to avoid duplication of effort. In its efforts to cooperate with parallel processes, the IRB will nonetheless remain independent of any influence or agenda of other institutional offices and will carry out its charge to resolve promptly any allegations of non-compliance.

## 10. Suspension or Termination of Research

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the requirements or determinations of the IRB or that has been associated with unexpected serious harm to the research participants. When the IRB suspends or terminates approved research, the IRB is responsible for promptly reporting the suspension or termination and the reasons for doing so to the Investigator, the Institutional Official, to OHRP and/or the FDA when applicable, and as required by the regulations (45 CFR 46.113 and [21 CFR 56.113](#)).

### Defined Terms:

**Suspension:** A temporary halt in some or all research activities.

**Termination:** A permanent stop to some or all of the research activities.

**Investigator-Initiated Voluntary Hold:** An Investigator voluntarily suspends or terminates some of all of the activities of an approved protocol.

### Investigator Reporting Requirements

Investigators are required to report to the IRB when the decision is made to voluntarily suspend or terminate research (e.g., a voluntary hold). Investigators ordinarily make these decisions at the recommendation or direction of a DSMB/C, research sponsor, or contract research organization, or based on their own assessment. Investigators should discuss with the IRB Director the most appropriate reporting mechanism (e.g., event report, amendment, study closure). Investigator-initiated voluntary holds may require reporting to authorities if the IRB finds that there is serious or continuing non-compliance or unanticipated problems involving risks to the subjects or others underlying the voluntary hold, or if required by the Sponsor or oversight bodies.

### IRB Determinations

Determinations to suspend or terminate the approval of a research study are ordinarily based on the occurrence of unanticipated problems involving risks or harms to participants or others, or serious or continuing non-compliance on the part of the Investigator or the research team. Suspensions or terminations are ordinarily determined at a convened IRB meeting, however the IRB Chair, on behalf of the IRB, or Institutional Official, on behalf of the CRC, may suspend a protocol on an urgent basis when an event occurs between scheduled IRB meetings and there is sufficient evidence to indicate that a suspension is necessary to protect the rights, welfare and safety of the research participants.

A suspension or termination by the IRB may be comprehensive (i.e., encompass all aspects of a research study) or partial (i.e., the suspension of enrollment of new participants). The IRB may impose the corrective actions it deems necessary to ensure that the circumstances that formed the basis for the suspension or termination are mitigated and prevented in the future.

The convened IRB will determine and document the reasons for suspending or terminating the research. If the research has been suspended or terminated outside of the IRB meeting (e.g., by the Chair or IO), the IRB will review the suspension or termination at its next convened meeting. In its deliberations, the IRB will consider the appropriate actions to protect the rights and welfare of currently enrolled subjects (e.g., follow-up or continuing medical care, assigning a new PI, independent monitoring, etc.), including informing current subjects of the suspension or termination.

The IRB staff or Chair will ordinarily notify the Investigator of determinations to suspend or terminate the research immediately following the convened meeting at which the determination was made. A letter from the IRB will be sent to the Investigator within 5 business days, outlining the IRB's determination and required corrective action plan.

The IRB will follow its policy on ‘Reporting Incidents to Institutional Officials and Regulatory Agencies’ in determining appropriate notifications of the suspension or termination to others. Investigator-initiated suspensions or terminations are not ordinarily considered to be reportable events unless the IRB determines that serious and/or continuing noncompliance or unanticipated problems involving risks to subjects or others have occurred in the research.

### **Appeals**

Investigators have the opportunity to respond to the suspension or termination and offer new procedures or a new research plan to protect the rights, safety and welfare of the participants, which will be considered by the IRB, in conjunction with the Investigator’s implementation of any required corrective actions, in evaluating whether the research may be allowed to be re-activated (in the case of suspension) or re-approved (in the case of terminations) at a later date. Investigators wishing to appeal a suspension or termination may do so in writing to the IRB Chair or IO. The terms or conditions for an appeal (e.g., response time, corrective actions, additional approvals, etc.) will be documented on the IRB suspension/termination letter.

### **Notification to Research Subjects**

Depending upon the nature of the suspension or termination and the potential risk to participants, the IRB may require any of the following to ensure the seamless care of research participants and the mediation of any risk presented by the suspension, termination, or the underlying circumstances that led the IRB to suspend or terminate the research:

- Notifications to the subjects
- Re-consent using a modified informed consent form before continuation in the study
- Notifications to the subject’s health care provider
- If subjects are enrolled in a clinical study involving a test article (drug or device) or treatment of any kind, procedures may include:
  - tapering-off of a drug or device
  - a final study visit that may involve laboratory tests or physical exams
  - arrangements for continued care or treatment by the subject’s physician or a referral to an appropriate physician or another Investigator
- Additional subject follow-up and reports to the IRB for a period of time beyond that originally contemplated in the protocol
- Temporary or permanent transfer of the responsibility of the research to another Investigator
- Other procedures or corrective actions as determined by the IRB.

Ordinarily, subject notifications will be written and signed by the Investigator and reviewed and approved by the IRB at a convened meeting, or by expedited procedures (as determined by the IRB). However, on occasion, the IRB may write and send such a letter from the IRB or Institution, with the guidance of the Institutional Official and/or General Counsel and/or the Investigator.

## 11. Populations Vulnerable to Coercion or Undue Influence and Special Protections

Under the Revised Common Rule at 45 CFR 46.111(a)(3) and (b), the regulations require that when the research participants are “likely to be vulnerable to coercion or undue influence, such as children, prisoners, and individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these individuals.” The CRC IRB affords additional protections for vulnerable persons, as described in this policy section.

### 11.1 Research with Pregnant Women

The CRC IRB applies additional protections for research involving pregnant women in accordance 45 CFR 46, Subpart B and applies when pregnant women are the focus of the research and regardless of funding source. The CRC IRB does not review research involving fetuses, neonates or uncertain viability, and non-viable neonates.

**Pregnancy:** The period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

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

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses
- Any risk is the least possible for achieving the objectives of the research and one of the following applies:
  - The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus
  - If there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means
- The consent of the woman is obtained in any of the following circumstances:
  - The research holds out the prospect of direct benefit to the pregnant woman,
  - The research holds out the prospect of a direct benefit both to the pregnant woman and the fetus
  - The research offers no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means
- The consent of both parents must be obtained for research that holds out the prospect of direct benefit solely to the fetus, with the following exceptions:
  - The father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity
  - The pregnancy resulted from rape or incest
- Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate
- For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part
- No inducements, monetary or otherwise, will be offered to terminate a pregnancy
- Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy
- Individuals engaged in the research will have no part in determining the viability of a neonate.

### 11.2 Research with Prisoners



Under 45 CFR 46 Subpart C, extra protections are provided for research participants who are prisoners, and additional responsibilities for the IRB Office. Research involving prisoners cannot be exempt from IRB review.

### **Important Definitions:**

- **Prisoner:** Any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.
- **Minimal Risk:** The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. Note: The definition of “minimal risk” under 45 CFR 46.303(d) for research involving prisoners is different than the definition of “minimal risk” under 45 CFR 46.102(j) for research involving subjects who are not prisoners.

### **Examples of Individuals who are considered to be prisoners under the regulations:**

- Individuals who are detained in a residential facility for court-ordered substance abuse treatment as a form of sentencing or as an alternative to incarceration
- Individuals with psychiatric illnesses who have been committed involuntarily to an institution as an alternative to a criminal prosecution or incarceration
- Parolees who are detained in a treatment center as a condition of parole Adolescent detained in a juvenile detention facility

### **Examples of Individuals who are NOT considered to be prisoners under the regulations:**

- Individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community
- Individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness or who have been civilly committed to non-penal institutions for treatment because their illness makes them a danger to themselves or others Individuals living in the community and sentenced to community-supervised monitoring, including parolees
- Probationers and individuals wearing monitoring devices are generally not considered to be prisoners; however, situations of this kind require an analysis of the particular circumstances of the planned subject population. The CRC IRB may consult with OHRP about research involving these populations.

### **Convened Meeting Review**

When research involving prisoners is reviewed at a convened meeting, the following criteria must be met:

- A majority of the IRB (exclusive of prisoner members) have no association with the prison involved, apart from their membership on the IRB.
- At least one IRB member who is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity is present at the meeting. If the prisoner representative cannot be present, research involving prisoners cannot be reviewed or approved.
- The prisoner representative may attend the meeting by phone, videoconference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.
- The prisoner representative will review research involving prisoners, focusing on the requirements in 45 CFR 46 Subpart C or equivalent protections.
- The prisoner representative will receive all review materials pertaining to the research prior to the meeting and with enough time to review the materials for the meeting.
- The prisoner representative will use the “Research Involving Prisoners” checklist as part of their review
- The prisoner representative must present their review either orally or in writing at the convened meeting where the research involving prisoners is reviewed.

- Modifications involving more than a minor change reviewed by the convened IRB will be reviewed by the same procedures used during the initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting.
- Continuing review will follow the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting
- If no subjects have been enrolled, the research may receive continuing review using the expedited procedure under expedited category #8.

### **Expedited Review**

Research involving interactions with prisoners may be reviewed by the expedited procedure if:

- The research involves no greater than minimal risk for the prison population being studied
- The prisoner representative agrees with the determination that the research involves no greater than minimal risk
- The prisoner representative serves as a reviewer, or as a consultant. The prisoner representative may serve as the sole reviewer or in addition to another reviewer, as appropriate.
- Review of modifications and continuing review must use the same procedures for initial review using this expedited procedure including the responsibility of the prisoner representative
- The reviewer will use the “Research Involving Prisoners” checklist as part of their review

Research that does not involve interactions with prisoners (e.g. existing data, record review) may be reviewed by the expedited procedure if:

- The research is not greater than minimal risk for the prison population being studied
- Review by a prisoner representative is not required
- The prisoner representative may review the research as a reviewer or consultant
- Review of modifications and continuing review must use the same procedures as initial review
- The reviewer will use the “Research Involving Prisoners” checklist as part of their review

### **Subjects who are Imprisoned while Enrolled in Research**

If a subject becomes a prisoner while enrolled in a research study that was not previously reviewed in accordance with 45 CFR 46 Subpart C, the IRB will:

- Confirm that the participant meets the definition of a prisoner.
- Terminate enrollment or review the research study under Subpart C if it feasible for the subject to remain in the study.
- Before terminating the enrollment of the incarcerated subject, the IRB will consider the risks associated with terminating their participation in the study.
- If the subject cannot be terminated for health or safety reasons:
  - keep the subject enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform the Office for Human Research Protection (OHRP) of the decision along with the justification. OR
  - Remove the participant from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.
- If a subject is incarcerated temporarily while enrolled in a study:
  - If the temporary incarceration has no effect on the study, keep the subject enrolled.
  - If the temporary incarceration has an effect on the study, handle according to the above guidance for when a subject becomes a prisoner enrolled in a research study
- Investigators are required to report to the IRB within 5 days of knowing that a subject has become a prisoner. In this circumstance, Investigators should use the CRC IRB Event form for their reporting.

### **Permissible Research Involving Prisoners**

Research involving prisoners is only permissible if the research involves one (or more) of the categories listed below.

- (a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:
- (1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under [§46.305](#) of this subpart; and
  - (2) In the judgment of the Secretary the proposed research involves solely the following:
    - (i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
    - (ii) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
    - (iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
    - (iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.
- (b) Except as provided in [paragraph \(a\)](#) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Epidemiologic Studies where the sole purposes are one of the following:

- To describe the prevalence or incidence of a disease by identifying all cases.
- To study potential risk factor associations for a disease.
- The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
- Prisoners are not a particular focus of the research.

#### **Additional Approval Criteria for Research Involving Prisoners**

In order to approve research involving prisoners, the IRB must make all of the following additional findings:

- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.
- Unless the principal investigator provides justification in writing for following some other procedures, control participants are selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole.
- When there is a need for follow-up examination or care of participants after the end of their participation, adequate provisions are made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Note: The above criteria must be made in addition to the regulatory criteria for approval as required by 45 CFR 46.111 21 CFR 56.111.

### **Documentation and Certification**

Findings related to the additional protections for research involving prisoners will be documented in either the IRB minutes (convened meeting review) or the IRB file (expedited review). For research that is federally funded, the CRC IRB will certify to the DHHS Secretary through OHRP that the IRB reviewed the research and made the findings as required by the federal regulations. The Institutional Official, IRB Chair, and/or IRB Director will forward the certification request to OHRP. The certification will include the following:

- IRB-approved protocol
- Applicable IRB forms/applications
- Other materials that were reviewed by the IRB
- BU CRC IRB's FWA number
- IRB Registration number
- The date in which the protocol was considered, including a brief chronology that includes the date of initial IRB review and the date of subpart C review, if not done at the time of initial IRB review.

### **11.3 Research with Children**

Under 45 CFR 46 subpart D, additional responsibilities are required for IRB review, and extra protections are put into place when conducting research with children.

#### **Defined Terms**

**Assent:** A child's affirmative agreement to participate in research. Note: Failure to object should not, absent affirmative agreement, be construed as assent.

**Children:** Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In Massachusetts, individuals under the age of 18 are considered minor children unless they meet one of the exceptions as defined by Massachusetts law.

**Guardian:** An individual who is authorized under applicable State and local law to consent on behalf of a child to general medical care.

**Minimal Risk:** The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**Minor Increase of Minimal Risk:** Slightly more than minimal and pose no significant threat to the child's health or well-being.

**Parent:** A child's biological or adoptive parent.

**Permission:** The agreement of parent(s) or guardian to the participation of their child or ward in research.

#### **Permissible Research Involving Children**

The CRC IRB applies additional protections for research involving children in accordance with 45 CFR 46, Subpart D and 21 CFR 50 Subpart D. Children may be involved in research if the research falls into one of the categories below:

Category 1 (45 CFR 46.404/21 CFR 50.51):

- Research is not greater than minimal risk
- Adequate provisions are made for soliciting the assent of the children and the assent of the parent(s) or guardian

#### Category 2 (45 CFR 46.405/21 CFR 50.52)

- Research involves greater than minimal risk
- The research presents the prospect of direct benefit
- The risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject or by a monitoring procedure that is likely to contribute to the subject's well-being
- The risk is justified by the anticipated benefit to the subjects
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as presented by available alternative approaches
- Adequate provisions are made for soliciting the assent of the children
- Adequate provisions are made for soliciting the permission of the parent(s) or guardian

#### Category 3 (45 CFR 46.406/21 CFR 50.53)

- The risk represents a minor increase over minimal risk
- 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;
- The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition
- Adequate provisions are made for soliciting assent of the children
- Adequate provisions are made for soliciting the permission of the parents or guardians

#### Category 4 (45 CFR 46.407/21 CFR 50.54)

If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to HHS or the Commissioner of Food and Drugs (if FDA-regulated) for review. The research may proceed only if the Secretary, HHS, or his or her designee, or the Commissioner of Food and Drugs (if FDA-regulated) after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408

#### **Assent for Research Involving Children**

Adequate provisions for soliciting assent of a child to participate in research are required when the child is capable of providing assent. When determining whether children are capable of assent, the IRB will take into account the ages, maturity, health and well-being of the children involved. The IRB's determination of the children's capacity to consent may apply to some or all of the children in the proposed study. If assent is not a requirement of some of the children, the IRB will indicate which children are not required to assent. Generally, the IRB does not require assent for children aged 5 years and younger.

#### Documentation of Assent

The IRB recommends documentation of assent as follows:

- Parental Permission for children under 6 years of age

- Verbal assent for children ages 6-11
- Written assent from children ages 12-17 (unless verbal consent is approved for the parents/legal guardians/adult subjects). Children aged 12-17 may sign either a separate assent form or sign the same consent form that is signed by their parent(s) or legal guardian(s).

#### Waiver of Assent

The IRB may determine that a waiver of children's assent is appropriate if one of the conditions below applies:

- If the capability of some or all of the children is so limited that they cannot reasonably be consulted
- If the intervention or procedure involved in the research holds out the prospect of direct benefit to the health or well-being of the children and is available only in the context of the research
- If the research meets the same conditions as those for waiver or alteration of informed consent in research involving adults, as specified in the regulations at either 45 CFR 46.116(c) or 45 CFR 46.116(d)

#### **Parental Permission**

Adequate provisions for soliciting the permission of the parent(s) or legal guardian(s) is required for children to participate in research as stipulated below, unless the IRB determines that these requirements can be waived:

- For research approved under Categories 1 and 2 (listed above), permission of one parent is sufficient
- For research approved under Categories 3 and 4 (listed above), both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
- When permission for a child to participate in research is to be obtained from a legal guardian(s) rather than from the child's biological or adoptive parent(s), the guardian must provide documentation of the legal ability to consent to the child's general medical care. The IRB and Investigators will consult with General Counsel as necessary.

#### Documentation of Parental/Legal Guardian Permission

Parental permission should be documented in accordance with 45 CFR 46.117 unless the IRB waives the requirement for documentation of consent under one of the options listed below:

##### Option 1

- The research is not FDA regulated
- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality

##### Option 2

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

#### Waiver of Parental/Legal Guardian Permission

The IRB may waive the requirement for parental permission using the following options:

##### Option 1

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

### Option 2

- The research is not FDA regulated
- The research involves no more than minimal risk to the subjects
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver or alteration
- Whenever appropriate, subjects will be provided with additional pertinent information after participation. If the investigator is not providing this information, he/she must provide the rationale for why it is not necessary to provide additional information after participation.

### Option 3

A research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the requirement for parental permission, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law.

In determining an appropriate mechanism for protecting children, the IRB will consider the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

### **Wards of the State**

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under Categories 3 and 4 only if the research is:

- Related to their status as wards OR
- Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research is approved under Category 3 or 4, the IRB will require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate will be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization. The IRB will consult with General Counsel, as needed.

### **Children who Reach the Legal Age of Consent While Enrolled in a Study**

When a child who was enrolled in research with parental or guardian permission subsequently reaches the legal age of consent, the subject's participation in the research is no longer regulated by the requirements regarding parental or guardian permission and subject assent. Legally effective informed consent must be obtained (unless waived by the IRB) from the now-adult subject for any continued participation (including analysis of individually identifiable data or specimens) in the study.

### **Reimbursements to Children and/or Parents**

The IRB will review reimbursements to children and parents to ensure that the reimbursements are age-appropriate and not coercive. Generally, the IRB recommends that children be reimbursed in the form of a gift card or other token instead of cash. The reimbursement amount and schedule should be designed so that it is not a factor in the child's decision whether to participate or the parent's decision to give permission for a child's participation.

### **Special Considerations**

Under Massachusetts Law the following individuals under the age of 18 are subject to exceptions that take

them out of the definition of children (as defined on page 1 of this policy), including those who are:

- Married/widowed/divorced
- A parent
- A member of the armed forces
- Are living separate and apart from a parent or guardian and managing their own financial affairs
- In the case of a female, pregnant or believes herself to be pregnant, unless the procedures involve abortion, a female under the age of 18 who is not and has never been married meets the definition of “children” as defined on page 1 of this policy
- Seeking care for a disease defined under Massachusetts law to be dangerous to the public health (the right to consent is limited to the diagnosis and treatment of the disease)

#### **11.4 Research with Persons with Impaired Decision-Making Capacity**

The CRC IRB applies additional protections for approving research involving persons with impaired decision-making capacity.

##### **Defined Terms**

**Capacity to consent:** The ability to provide legally effective consent to enroll in a research study (AAHRPP definition)

**Limited Decision-Making Capacity:** Substantial impairment of cognitive functions (e.g. attention, comprehension, memory, and intellect), or conditions that affect a person’s ability to make effective and informed decisions about participating in a research study.

**Legally Authorized Representative:** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research [45CFR46.102(i)].

##### **Permissible Research Involving Persons with Impaired Decision Making Capacity**

The IRB will ordinarily approve research involving individuals with impaired decisional capacity if the research meets one of the criteria below:

- The research is related to the participant’s condition or circumstance;
- The research meets one of the following criteria:
  - Presents no greater than minimal risk to the participants
  - Presents an increase over minimal risk to participants, but offers the potential for direct individual benefit to the participants
  - Presents a minor increase over minimal risk to participants and does not have the potential for direct individual benefit but is likely to contribute to generalizable knowledge about the participant’s condition or circumstance.
- The investigator must provide the rationale for why individuals with impaired decision-making capacity should be included as participants in the research study.

When enrolling persons in research who may have impaired decision-making capacity, the Investigator must identify in the IRB application how they will determine whether a participant has the capacity to consent (e.g. standardized assessments) to their own participation and, when the person does not have the capacity to consent, who will serve as the Legally Authorized Representative (LAR) and the process for obtaining consent from the LAR and assent from the participant, as applicable.



### **Assent of Participants**

When participants do not have the capacity to consent to their own participation in the research, but they the ability to provide some judgment concerning the nature of the research and their participation in it, the Investigator should obtain the participant's assent in addition to the consent of their LAR. The IRB will determine when the assent of some or all of the participants is required and the appropriate method (if any) for documenting assent. A potential participant's objection to the research in any form (verbal, non-verbal) must be respected. Furthermore, once consented, even if by a LAR, if the participant at any time objects to participating or continuing in the research, that objection must be respected, and participation withdrawn.

If participants may regain the capacity to consent during the study, the protocol and informed consent process should include a mechanism for obtaining the participant's subsequent direct informed consent to participate in the research. If a participant regains decision making capacity and declines to continue in the research, the participant must be withdrawn from the research.

Conversely, some studies may involve populations where participants have the capacity to consent at the beginning of the research study but may lose that decisional capacity during the study. In such circumstances, the Investigator must document in the IRB application how a LAR will be identified, how their consent will be obtained, and the assent of the participant to confirm their continued interest in participating in the study. Ideally, this process will be discussed with the participant at the beginning of the study, and an anticipated LAR will be identified at that time.

### **Informed Consent of Legally Authorized Representatives**

LARs should be informed that, where possible, their decision to consent to participation should be guided by their knowledge of the beliefs, views, and preferences of the participant. The LAR should be fully informed of the risks, benefits and alternatives to the research. If the beliefs, views, and preferences of the participant are not known, the LAR should act in the best interest of the participant.

Under Massachusetts law, consent must come either from the legal guardian of the participant, or from the participant's health care agent (either as appointed under the Massachusetts health care proxy law, or as identified by a health care provider under the common law for obtaining consent to the provision of medical care and associated procedures).

The CRC IRB will allow consent to be obtained from the following persons, in the following order:

- A court appointed guardian who has clear authority to make health care decisions for the individual;
- A person designated as a health care agent under a valid health care proxy, with express authority to make health care decisions;
- A durable power of attorney with express authority to make health care decisions;
- A family member: including a competent spouse, adult child, or competent parent.

Note: If the person legally responsible for providing informed consent does not consent to the subjects' participation in the research, no other person on the above list may approve participation.

When the research will take place in other states or countries, the Investigator (or a relying IRB) must provide information on local context issues pertaining to LARs, informed consent, and assent of individuals with impaired decision-making capacity – including laws, regulations and/or policies, that may differ from the CRC IRB policies and procedures.

Consent should be documented in accordance with the CRC IRB policies on informed consent.

### **IRB Considerations of Additional Safeguards**

In reviewing an IRB application and/or a protocol that involves the enrollment of persons with impaired decision-making capacity, the IRB will consider requiring additional safeguards, as appropriate, including:

- Engagement of a person with appropriate expertise to assess the capacity of the potential participant(s) and who is not part of the research team;

- Use of standardized assessments of cognition and/or decisional capacity;
- Use of informational or educational techniques during the consent process to enhance understanding of the research;
- Engagement of an independent person to monitor the consent process (including recruitment, consent, consent capacity assessment, debriefing, etc.);
- Use of waiting periods to allow for additional time to consider information about the research study;
- Obtaining consent of a LAR;
- Assent of the participant (in addition to consent of the LAR);
- Engagement of a research subject advocate;
- Explanation of the research, their participation in it and affirmed assent at each study visit;
- If participants may regain the capacity to consent, a plan to re-assess the participant’s capacity at different intervals during the study.

In its review, the IRB (via convened Board meeting, or expedited review procedures) will consider the appropriateness of the following, and document in the IRB meeting minutes and the reviewer worksheets, as applicable:

- How the Investigator will determine whether a participant has impaired decision-making capacity and when it may be necessary to seek informed consent from a LAR;
- Who is appropriate to serve as a LAR;
- The plan to approach the LAR for recruitment;
- The process for informed consent of the LAR and the assent of the participant;
- Whether the participant is able to provide assent to participate in the research and in what form this will take (e.g. verbal, written, one time, at each visit, etc.);
- Whether the capacity of the participant to provide informed consent may fluctuate during the course of the research, and the plan to assure continued informed consent/assent during the research;
- The plan to withdraw participants if they indicate they do not want to participate in the research, when the LAR has provided informed consent;
- Any additional safeguards necessary to protect the rights and welfare of the participants.

The IRB will consult with General Counsel as needed when reviewing research protocols that involve persons with limited decision-making capacity to consent to research.

### **11.5 CRC Employees, Students, Post-Doctoral Trainees**

Although not listed specifically in the federal regulations as vulnerable subjects, the Office of Human Research Protections (OHRP) discusses employees under the heading of “Special Classes of Subjects” in its IRB Guidebook. The OHRP suggests that attention should be paid to the issues of voluntariness, undue inducement, and confidentiality and recommends avoiding individual solicitations to participate in research.

CRC employees, students and post-doctoral trainees may participate in any study for which they are eligible. However, in order to prevent any coercion (or perception of coercion) or undue pressure to participate, Investigators should not specifically recruit individuals who work directly or indirectly for them, nor should they recruit individuals for whom they have any educational or supervisory oversight. Instead, all recruitment should take place via public forums, such as bulletin boards, where those interested in participating may contact the Investigator to learn more information about the research. Research participation should not be offered as extra compensation, credit or as a factor in job promotion or advancement unless an alternative non-research option for receiving such benefit is also made available at the same time.

Generally, Investigators will not be allowed to recruit, consent, or conduct study procedures on/with their own students or employees. There may be exceptions to these requirements if the research is not more than minimal risk, the investigator provides sufficient justification and provides appropriate assurances and protections for the students and employees, as applicable, including:

- Investigators cannot directly ask their students/employees to participate in their research.
- Co-investigators or other appropriate study staff who do not have a direct academic or supervisory role with the student/employee will ordinarily conduct informed consent and study procedures and should have the only access to identifiable study data about the students/employees;
- There must be no effect on the student's grade(s), their status as a student or any effects on student's/employee's advancement and the consent form must provide a statement to this effect;
- The rationale for enrolling their students/employees should include why their participation is needed (e.g. why their students/employees and not other students/employees or participants external to BU).
- Any additional plans for protecting these subjects.

These exceptions will be reviewed by the IRB Chair and IRB Director and may involve an additional IRB member. In some instances, review of these exceptions will take place at a convened meeting. If the study is greater than minimal risk, an investigator ordinarily will not be allowed to enroll their own students unless the student would directly benefit from participation in the research.

### **11.6 Investigator Self-Experimentation**

The CRC IRB does not prohibit Investigator self-experimentation. However, the IRB will consider as part of its review the level of self-experimentation and the potential risks and benefits to the Investigator as a research participant.

One of the main concerns of the IRB is that the enthusiasm for a novel concept may outweigh an Investigator's concern for their own welfare. For this reason, the IRB may require that a department Chair or even an IRB member obtain informed consent from the Investigator. The IRB also may institute additional safeguards for the research project, such as shorter review periods and monthly progress reports.

### **11.7 Persons who are Economically or Educationally Disadvantaged**

The CRC IRB affords extra protections for persons who are economically or educationally disadvantaged by way of its recruitment, informed consent and IRB review policies and procedures, as documented throughout this policy manual (e.g. IRB Composition – section 2.4, Recruitment Guidelines – section 4.3, Payments to Participants – section 4.4, Documentation of Informed Consent – section 4.6, Witness to the Consent Process – section 4.10 and IRB Approval Criteria – section 5.3).

### **11.8 Subjects in Harmful Situations: Abuse, Suicide, and Threat of Harm**

Investigators, at times, conduct research or encounter situations where the subjects are at risk for harm, such as abuse, suicide, or threat of harm. In these circumstances, subjects may disclose information about abusive relationships, suicidal thoughts, or plans to harm others. For studies where these issues may arise, the IRB will require additional safeguards to protect subjects, such as:

- Confirmation of investigator qualifications to manage these situations.
- Obtaining a Certificate of Confidentiality or informing subjects of what circumstances would necessitate the investigators to disclose information outside of the study.
- Documenting a specific plan to deal with the potential situation (e.g., if the research involves persons with suicidal ideation, a plan for managing the process during the research – for the researchers, and the participants.)
- Including information in the consent form about when information can be disclosed outside of the study, inclusive of a description of what information will be disclosed.

Investigators may be mandated reporters in accordance with Massachusetts law. Mandated reporters may include those who work with children, elders, and persons with disabilities. To find out more information, please review the [Massachusetts District Attorney website on Reporting Abuse or Neglect of a Child, Elder,](#)

[or Person with a Disability](#) webpage. Investigators who work with BU students or employees may also be mandated reporters under Title IX and should review reporting requirements.

Independent of mandatory reporting requirements, investigators are responsible for protecting the rights and welfare of human subjects. This may include consulting with others who have experience with certain situations or referring the subject to resources that can help them. The IRB may consult with the Office of General Counsel on areas of mandatory reporting or disclosing information outside of a study.

## 12 FDA Regulated Research

FDA's regulations, including those governing IRB review, informed consent and protection of human subjects, may apply to research sponsored or conducted by or at CRC. A sponsor or sponsor-Investigator, as defined below, should determine whether proposed research is subject to FDA regulation. When in doubt, a sponsor or sponsor-Investigator may consult the IRB. If FDA regulations apply to proposed research, the sponsor or sponsor-Investigator may be obligated to submit to FDA an Investigational New Drug ("IND") or Investigational Device Exemption ("IDE") application prior to the commencement of the research. The following sections describe the use of investigational drugs and devices and other FDA regulated products in research otherwise under the auspices of CRC.

### Defined Terms

**Clinical Investigation:** Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA (i.e., it requires an IND or IDE to conduct the investigation), or is not subject to requirements for prior submission to the FDA under these sections of the act, but 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.

- With respect to investigational drugs, a clinical investigation is any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.
- With respect to investigational devices, a clinical investigation means research involving one or more human subjects to determine the safety and effectiveness of a device.

**Emergency Use:** Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

**Humanitarian Use Device (HUD):** A humanitarian use device is a device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. Although the use of a HUD within its approved labeling is not "research", a Humanitarian Device Exemption (HDE), similar to an IDE, is nonetheless required.

**Investigational Device:** A device, including a transitional device that is the object of a clinical investigation.

**Investigational Device Exemption (IDE):** To use an investigational device in the course of a clinical investigation, the sponsor (or sponsor-Investigator) is required to apply for and receive an IDE in accordance with 21 CFR 812.

**Investigational New Drug (IND):** A new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms investigational drug and investigational new drug are deemed to be synonymous. To use an investigational drug in the course of a clinical investigation, the sponsor (or sponsor-Investigator) is required to apply for and receive an IND from the FDA in accordance with [21 CFR Part 312](#).

**Investigator:** An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject).

**Medical Device:** An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

- Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or

prevention of disease, in man or other animals, or

- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

**Sponsor:** For purposes of this Section, a person or entity who takes responsibility for and initiates, but does not actually conduct, a clinical investigation. An entity that uses one or more of its employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-Investigator, and the employees are Investigators.

**Sponsor-Investigator:** An individual who both initiates and actually conducts a clinical investigation. The term includes a person, not a company.

**Significant Risk (SR) Device:** Significant risk device means an investigational device that:

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

**Non-Significant Risk (NSR) Device:** A non-significant risk device is an investigational device other than a significant risk device.

**Test Article:** Any drug, biologic, or medical device for human use, or human food additive, color additive, electronic product, or any other article subject to FDA regulations.

### **FDA Exemptions from IRB Oversight**

The following categories of clinical investigations may be exempt from the requirements of FDA regulations for prospective IRB review:

- Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review (see section 13.7), per [21 CFR §56.104\(c\)](#).
- Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture, per [21 CFR §56.104\(d\)](#). See Section 5.4 for the requirements and process for exempt research.

### **Considerations for FDA-Regulated Research**

- The informed consent must notify subjects that their medical records may be subject to review by the IRB, agents of the FDA and, in some cases, by agents of the commercial sponsor.
- When there is a commercial sponsor, indemnification of CRC by the Sponsor is required.
- Sponsor reporting forms should be modified where possible so that no names, initials or other identifiers are used when communicating research results. Separate research protocol numbers should be used to identify individual participants and only the Investigators should have the means to link the code numbers to identifiable patients.
- Research involving Investigational Drugs or Devices that are reviewed and approved by the CRC IRB will undergo Quality Assurance Review.

## 12.1 Research Involving Investigational Drugs

The CRC IRB ensures that research involving investigational drugs is conducted in accordance with applicable federal regulations at 21 CFR 312, 21 CFR 50, 21 CFR 56. When a new drug is being tested to determine safety and efficacy an Investigational New Drug (IND) application must be filed with the FDA. Research studies involving marketed drugs may also require an IND. The IRB will determine if an IND is required or if the study meets one of the criteria for an exemption from the IND requirements.

Investigators wishing to use drugs in research must submit to the IRB, as applicable:

- Investigator's brochure
- Drug package insert
- Summary of prior use/investigations
- FDA correspondence (including IND documentation)
- Sponsor Protocol, including the Sponsor Informed Consent Form
- Plan for receipt, storage, control, labeling, and dispensing of drug
- IRB Drug Form

The IRB will not approve the study until it has verification of the IND, or that it has been 30 days since the investigator submitted the IND to the FDA unless the sponsor receives earlier notice from the FDA. The pharmacist IRB representative will serve as a Reviewer on any study that involves an investigational drug.

### Exemptions from IND Requirements:

In order to be exempt from IND requirements, the study must fall into one of the following exemption categories, to be verified by the IRB:

#### Exemption 1

- The drug product is lawfully marketed in the United States.
- 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.
- 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.
- 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.
- The investigation is conducted in compliance with 21 CFR 50 and 56.
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

#### Exemption 2

A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:

- Blood grouping serum.
- Reagent red blood cells.
- Anti-human globulin.
- The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The diagnostic test is shipped in compliance with 21 CFR 312.160

#### Exemption 3

The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160.

#### **Exemption 4**

A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

#### **Drug Products not Manufactured and/or Compounded by a Licensed Pharmaceutical Company**

If the drug product is manufactured and/or compounded by an entity that is not a licensed pharmaceutical company, the IRB will require the following, as applicable:

- If a compound pharmacy will be used to prepare the drug product, the IRB will require that the pharmacy follow all rules and regulations of the Massachusetts Board of Pharmacy
- Procedures for compounding drugs
- Procedures for labeling drugs and shipping drugs to the research site
- Certificate of Analysis (COA)

#### **Control of Investigational Drugs**

Investigators are required to have procedures in place to control investigational drugs to ensure that they are used only in approved research protocols and under the direction of approved investigators. The IRB will review the plan for drug accountability, including receipt, control, storage, labeling, dispensing, and recordkeeping to determine that the plan is appropriate and adequate.

#### **Investigator Responsibilities**

Investigators must comply with FDA and IRB policies and are responsible for the following:

- Ensure that the clinical research is conducted according to the approved protocol and applicable regulations.
- Inform the subjects, including any persons used as controls, via the informed consent form, that the drugs/biologics are being used for investigational purposes.
- Administer the study drug or biologic only to subjects under the investigator's personal supervision or the supervision of a qualified co-investigator.
- Report problems in accordance with IRB policies and applicable regulations.
- Do not supply the study drug or biologic to any person not authorized to receive it (patient or another investigator).
- Provide for control of drugs.
- Maintain adequate records of the disposition of the study drug to include dates, quantity and use by subjects.
- Return any unused supply of study drug to the sponsor upon completion, suspension, termination or discontinuation of the research study.
- Permit the FDA to have access to and copy and verify records or reports made during the study.

#### **Requirements for Sponsor-Investigators**

If the investigator is also the sponsor of the drug, the investigator must also comply with the FDA regulations that pertain to Sponsors, including:

- Submit IND Application Form 1571 and other required documents to FDA (21 CFR 312.23)
- Submit annual reports of the progress of the investigation to the FDA (21 CFR 312.56)
- Comply with FDA regulations regarding emergency use (21 CFR 312.54)
- Review and evaluate the evidence that relates to the safety and effectiveness of the drug as it is obtained from each investigator (21 CFR 312.56)
- Discontinue the study if the investigational drug presents an unreasonable and significant risk to subjects (21 CFR 312.56)
- Keep investigator(s) informed of the safety and effectiveness of the drug (21 CFR 312.55)
- Notify the FDA, IRB, and other investigators if the study is discontinued (21 CFR 312.56)
- Send safety reports to the FDA and other investigators (21 CFR 312.32)
- Select qualified investigators based on training and experience (21 CFR 312.53)



- Obtain FDA Form 1572 from all investigators (21 CFR 312.53)
- Obtain a written statement that each investigator will conduct the study as outlined in the protocol (21 CFR 312.53)
- Maintain documentation of the financial interests from investigators, for the duration of any covered studies under the IND, plus 1 year following study completion (21 CFR 312.53)
- Require investigators to meet local IRB requirements (21 CFR 312.66)
- Terminate investigators participation when they fail to follow protocol (21 CFR 312.56)
- Select a monitor to oversee the progress of the investigation (21 CFR 312.53)
- Monitor the progress of all IND investigations (21 CFR 312.56)
- Label the investigational drug in accordance with FDA regulations (21 CFR 312.6)
- Promote and distribute the drug in accordance with FDA regulations (21 CFR 312.7)
- Ship investigational drugs only to investigators participating in the investigation (21 CFR 312.53)
- Maintain adequate records that show the receipt, shipment, or other disposition of the investigational drug (21 CFR 312.57)
- Require investigators to store the investigational drug in a secure area (21 CFR 312.69)
- Require that investigators maintain adequate drug records (21 CFR 312.62)
- Ensure that investigators return all unused investigational drugs (21 CFR 312.59)
- Maintain complete and accurate records of payments made to investigators (21 CFR 312.57)
- Require investigators to keep case histories on each individual administered the investigational drug or employed as a control in the investigation (21 CFR 312.62)
- Collect reports (financial, progress, safety, and final) from investigators (21 CFR 312.64)
- Ensure any electronic data and source documentation for the studies covered under the IND meets the same fundamental elements of data quality expected of paper records (21 CFR 11)

## 12.2 Use of Controlled Substances in Research

The use of controlled substances in research is subject to both state and federal requirements, largely to prevent diversion and abuse. Controlled substances in Massachusetts include those drugs (or immediate precursors) listed on Schedule I-V of the federal Controlled Substances Act of 1970 (“CSA”) as amended ([21 U.S.C. § 801 et seq.](#)), as well as Schedule VI drugs, defined under Massachusetts law as all prescription drugs not otherwise included in Schedules I-V. See [105 CMR 700.000](#) et seq. Schedule VI drugs, while not regulated by the DEA under federal law, are nonetheless considered controlled substances in Massachusetts.

In simpler terms, in Massachusetts any drug used as an intervention in a research study is considered a controlled substance and is classified into [Schedules I to VI](#) or as an investigational new drug/IND. The Massachusetts law, [Title 105 CMR 700.009](#), requires that every principal investigator (PI) who is conducting research involving any drug must be covered by a Massachusetts Controlled Substances Registration (MCSR) Research License. This means that drug research should not commence until the PI has an active MCSR Research License from the MDPH. ***In general, drugs that are being used in research pursuant to an IND will require a prescription and thus will fall under Schedule VI and qualify as a “controlled substance” in Massachusetts.***

Investigators using Schedule I-V drugs in research are required to hold both a federal Drug Control Registration (DEA Form 225, Researcher), as well as Massachusetts Controlled Substance Registration (MCSR) with the Massachusetts Department of Public Health (MDPH) as a “researcher”. Generally, licenses are (i) issued to an individual, who may authorize other individuals to operate under his/her license under certain circumstances; (ii) specific to drug schedules identified on the license, and further limited to specific drug codes applied for; and (iii) identify a specific location where the controlled substances are to be stored and must be amended when the location of storage changes.

Until January 2020, institutions conducting drug research could fulfill this requirement by obtaining and annually renewing institution-wide “umbrella” MCSR research licenses. **This is no longer the case, and**

**each PI at an institution must register for their own license.** The DEA will not grant an applicant a license until the applicant has already obtained a license from the MA DPH. Investigators using only Schedule VI controlled substances would not need to be registered with DEA but would still need to hold a controlled substance researcher registration from the MA Department of Public Health.

Special procedural rules apply to research involving Schedule I drugs, Schedule II narcotic drugs, and investigational drugs. Investigators planning to use Schedule I drugs in research must apply for a separate DEA registration and include a copy of the research protocol with the application. There are also additional requirements in Massachusetts before an Investigator can use Schedule II narcotics or an investigational drug studied pursuant to an IND. Please contact the IRB Office if you plan to use any of these substances in your research.

Note that there are specific storage, recordkeeping, inventory, and disposal requirements for all controlled substances in Schedules I-V; furthermore, they may be used only by specifically authorized individuals. These drugs must be stored in a securely locked, substantially constructed cabinet or other enclosure, access to which is limited, so as to prevent theft or diversion of the drug; a hard copy bound inventory log must be stored with the drugs. Schedule VI drugs do not need to be stored in a lockbox; they can be stored together on a shelf nearby to the lockbox or in an unlocked cabinet. In general, Schedule VI drugs should not be stored with Schedule I-V drugs.

For questions on the requirements and registration process, please contact the [MDPH MCSR](#), the CRC IRB Office and the [BU EHS Office](#). The BUMC IRB Office maintains very clear [guidance on this topic](#), as well.

### **12.3 Use of Devices in Research**

The CRC IRB ensures that research involving investigational devices is conducted in accordance with applicable federal regulations at 21 CFR 50, 21 CFR 56, and 21 CFR 812. When research is being conducted to determine the safety and effectiveness of a device, the IRB will determine whether the device fulfills one of the exemption criteria and, if not, whether it is a significant risk device (IDE required) or a non-significant risk device (subject to abbreviated requirements).

Investigators wishing to use devices in research must submit to the IRB, as applicable:

- Device Manual
- Instructions for Use (IFU)
- Summary of prior use/investigations
- FDA correspondence (e.g. IDE documentation)
- Sponsor Protocol, including the Sponsor Informed Consent Form
- IRB Device Form
- Device risk assessment from the Sponsor

#### **Device Studies**

There are three types of device studies that are described in the FDA regulations at 21 CFR 812: exempt, non-significant risk, and significant risk, each described in more detail below.

#### **Exempt**

Under 21 CFR 812.2(c), a device can be exempt from the IDE requirements if it fits into one of the following categories:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in

- the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    - i. Is noninvasive
    - ii. Does not require an invasive sampling procedure that presents significant risk Does not by design or intention introduce energy into a subject
    - iii. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
  4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk.
  5. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.
  6. A device intended solely for veterinary use.
  7. A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
  8. A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Studies that are determined to be exempt from IDE regulations must still undergo review by the CRC IRB.

#### **Non-Significant Risk/Significant Risk Determination**

If a device is not determined to be exempt, it must be categorized as either non-significant risk (NSR) or significant risk (SR). The Sponsor is responsible for making the initial risk determination. The convened IRB will conduct an independent review of the study and the device to determine if the device is NSR or SR. If the FDA has already made the NSR or SR determination for the study, their determination is final. The NSR/SR determination will be documented in the minutes. If the IRB disagrees with the Sponsor's determination, the IRB will notify the investigator of this determination. The IRB will consult with the FDA as necessary.

The IRB will consider the following when making the NSR/SR determination:

- How the device will be used in the investigation, and not on the device alone
- Whether potential harm to participants could be life-threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention to preclude permanent impairment or damage
- Whether Potential harms to participants may occur as a result of additional procedures undergone as part of the research study

#### **Significant Risk Devices**

Investigations using Significant Risk devices must follow all the IDE regulations at 21 CFR 812 and have an IDE Application approved by the FDA before the study may proceed. The CRC IRB will not approve the study without documentation of the approved IDE.

#### **Non-Significant Risk Devices**

If the IRB determines that the device is a non-significant risk (NSR) device, an IDE application does not need to be submitted to the FDA. If the study using the NSR is approved by the CRC IRB, the study must fulfill the abbreviated requirements of the IDE regulations which include:

- The device is not a banned device
- The Sponsor labels the device in accordance with 812.5
- The Sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval
- The Sponsor ensures that each investigator participating in an investigation of the device obtains from

each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c)

- The Sponsor complies with the requirements of 812.46 with respect to monitoring investigations;
- The Sponsor maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10)
- The Sponsor ensures that participating investigators maintain the records required by 812.140(a) (3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
- The Sponsor complies with the prohibitions in 812.7 against promotion and other practices.

### **In-Vitro Diagnostic (IVD) Studies**

In vitro diagnostic products are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVD's are considered to be medical devices and are therefore subject to the FDA regulations that govern investigational devices (IDE regulations).

An IVD study may be exempt from the IDE regulations if it fits into one of the 3 categories below:

1. The IVD is a pre-amendment device (i.e. a device that was in commercial distribution prior to the enactment of the 1976 Medical Device Amendments to the Act), other than a transitional device, and is used or investigated according to the indications in the labeling at the time.
2. The IVD is a device, other than a transitional device, that has been found to be substantially equivalent to a pre-amendments device and is used or investigated according to the indications in the labeling reviewed by FDA in determining the substantial equivalence.
3. The IVD meets ALL of the criteria below:
  - i. Is properly labeled in accordance with 21 CFR 809,10(c).
  - ii. Is noninvasive\*.
  - iii. Does not require an invasive sampling procedure that presents significant risk does not by design or intention introduce energy into a subject.
  - iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

\*A noninvasive device is one that does not by design or intention:

- Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra OR
- Enter the body beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os
- Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive

If the IVD study does not fit into one of the three categories listed above, the study must have an approved IDE before the study can begin. The requirements for an IDE depends on the level of risk that the study presents to subjects. Refer to the "Non-Significant Risk/Significant Risk Determination" section of this policy for the IDE requirements. All studies of investigational IVD's (regardless of risk determination) that will support applications to the FDA are subject to 21 CFR 50 (Protection of Human Subjects) and 21 CFR 56 (Institutional Review Boards).

The FDA has issued guidance that the FDA will not require informed consent for the use of an IVD to analyze leftover human specimens providing that ALL of the following are true:

- The investigation meets the IDE exemption criteria at 21 CFR 812.2 (c)(3)
- The study uses leftover specimens collected for routine clinical care or analysis and/or specimens obtained from specimen repositories or leftover specimens that were previously collected for other research purposes

- The specimens are not individually identifiable. If the specimen is coded, it will be considered to be not individually identifiable if neither the investigator nor any other individuals associated with the investigation or the sponsor can link the specimen to the subject from whom the specimen was collected, either directly or indirectly through coding systems
- The specimens may be accompanied by clinical information as long as this information does not make the specimen source identifiable to the investigator or any other individual associated with the investigation
- The individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation
- The specimens are provided to the investigator without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information
- The study has been reviewed and approved by the IRB

Research on IVDs may be reviewed using the expedited procedures providing that the research meets all the requirements.

### **Control of Investigational Devices**

Investigators are required to have procedures in place to control investigational devices so that they are used only in approved research protocols and under the direction of approved investigators. The IRB will review the plan for device accountability, control, storage, labeling, dispensing, and recordkeeping to determine that the plan is appropriate for the study.

### **Investigator Responsibilities**

Investigators must comply with FDA and IRB policies and are responsible for the following:

- Maintain complete, accurate, and current records which include:
  - Any correspondence with other investigators the IRB, the sponsor, a monitor, or FDA Record of receipt, use, or disposition of the device
  - Records of each subject's case history and exposure to the device, including the date and time of each use
  - All relevant observations, including adverse device effects
  - Documentation of informed consent
- Obtain IRB approval prior to initiating the study
- Comply with the IRB-approved protocol
- Obtain informed consent of subjects prior to conducting study procedures
- Supervise device use
- Complete and submit applicable financial disclosures

### **Requirements for Investigators who are also Sponsors (Sponsor-Investigator)**

If the investigator is also the sponsor of the device, the investigator must also comply with the FDA regulations that pertain to Sponsors. Below is an overview of the major responsibilities. The overview is divided into Significant Risk Device Studies and Non-Significant Risk Device Studies.

- Significant Risk Device Studies
  - Obtain FDA and IRB approval for IDE (21 CFR 812.42)
  - Select investigator(s) with appropriate training and experience (21 CFR 812.43)
  - Select monitor in accordance with FDA regulations (21 CFR 812.43)
  - Ship investigational devices only to qualified investigators (21 CFR 812.43)
  - Obtain a signed agreement from the investigator using the required FDA documents (21 CFR 812.43)
  - Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations (21 CFR 812.45)
  - Ensure that investigator(s) are complying with FDA, IRB, and sponsor requirements (21 CFR 812.46)

- Conduct an evaluation of unanticipated adverse events and terminate the study if necessary (21 CFR 812.46)
  - Resume terminated studies only after receiving approval from the FDA and IRB (21 CFR 812.46)
  - Maintain accurate and complete records in accordance with FDA regulations (21 CFR 812.140)
  - Provide required reports to IRB, investigator(s), and FDA in a timely manner (21 CFR 812.150)
  - Label the device in accordance with FDA requirements (21 CFR 812.5)
  - Promote the device in accordance with IRB and FDA requirements (21 CFR 812.7)
- Non-Significant Risk Device Studies
    - Label the device in accordance with FDA requirements (21 CFR 812.5 9)
    - Obtain IRB approval of the investigation as a nonsignificant risk device study and maintain IRB approval during the investigation (21 CFR 812.2)
    - Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver (21 CFR 812.2)
    - Comply with FDA requirements for monitoring the study (see items above for monitoring requirements) (21 CFR 812.46)
    - Maintain accurate and complete records in accordance with FDA regulations, and report the results to the FDA, IRB, and investigators (21 CFR 812.140)

## **13 Community Engagement and Information for Research Participants and Family Members**

Before, during or after participating in a research study, individual participants or their family members may have questions, concerns, or complaints, or may want to know their rights as a participant in research. This section provides basic information that prospective and current research participants, as well as family members or others who may consent on behalf of a loved one or who may simply be consulted by a family member or friend who is considering participating in research, can expect to be provided by CRC Investigators.

### **13.1 Community Engagement**

The CRC IRB provides information and resources about research, participants rights, and the research process to participants, potential participants, researchers, and the community at-large. The CRC IRB engages with the community by providing resources about research and research participant rights on the CRC IRB webpage, requesting feedback from participants via an online anonymous survey on their experiences and suggestions on how to provide adequate resources and support to current and prospective participants, and by partnering with BU CRC departments that regularly see patients/participants as part of their university operations.

#### **CRC IRB Webpage**

The following information is included on the CRC IRB Webpage:

- Contact information for the IRB staff Information on research participant rights
- Links to common questions prospective participants may want to ask as part of their decision- making process about whether to participate in research
- Information and links on the types of research in which people most commonly participate Links to common terms used in the research context
- Links to the resources for participants, including: Boston University Research
- Office for Human Research Protections (OHRP) ClinicalTrials.gov
- Center for Information and Study on Clinical Research Participation (CISCRP)
- Information on what to do and who to contact with concerns or complaints about research at BU A link to a Research Participant Feedback Survey

#### **CRC IRB**

The CRC IRB requires that all consent forms and information sheets include the telephone contact number of the IRB. Research participants must be informed that they can contact the IRB if they have questions about their rights as a research participant or if they want to speak with someone independent of the research team. The IRB Consent Form template includes a link to the IRB website and while it is not required that investigator's use the template, the IRB may require the investigator to add a link to the IRB website and/or other information to the consent form/study documents to provide information about participating in research studies, available resources, and additional contact information for research participants. The IRB may waive this requirement for situations in which this would not be applicable. For example, if the research is being conducted outside of the United States and the research subjects don't speak English and may not have access to calling the United States.

The CRC IRB conducts education to the CRC research community on the rights of research participants, regulatory requirements, best practices and IRB processes. Investigators may request education be provided for their research staff or participants. Outside organizations may also request that the CRC IRB provide education.

At the time of IRB review, the IRB considers whether the criteria for equitable selection of subjects has been met. The IRB considers the following:

- How are participants recruited?

- Are there screening procedures? If so, are they appropriate for the selection of participants? Are costs and payments reasonable?
- Are the eligibility criteria clear and appropriate?
- Are there populations that are vulnerable to coercion and undue influence? What is the plan to mitigate coercion/influence?
- If there is exclusion of women, under-represented populations, or vulnerable persons is there rationale for their exclusion?
- Will participants receive the results of the research?
- If participants do not speak English, have all documents been translated to the appropriate language and is there a process to provide a translator for study visits?

The CRC IRB will work with CRC offices/departments that see clients and patients (e.g. Physical Therapy, Social Work, Center for Anxiety Related Disorders, etc.) to develop additional outreach efforts to educate the community about participating in research.

### **Assessment of Community Outreach Efforts**

The Associate Vice President, Research Compliance and CRC IRB Director in consultation with the CRC IRB Chair will assess the outreach efforts on an annual basis and will implement changes as necessary. The assessment may include feedback from Deans, Department Chairs, researchers/research staff, research participants, and community organizations.

### **13.2 Research Participant Rights**

Research participants and their legally authorized representatives should be aware of their rights:

- To be treated in a caring and polite way;
- To be told what the study is trying to find out;
- To be informed what will happen and whether any of the procedures, drugs or devices used in the research are different from what would be used in standard medical care;
- To be told about possible side effects or discomforts that may occur during the study;
- To be told if participants can expect any benefit from being in the study and, if so, what the benefit might be;
- To be told of other choices for treatment that they have, and how these alternatives might be better or worse than being in the study;
- To be told what sort of treatment is available if any medical problems arise;
- To be allowed to ask any questions about the study both before agreeing to be involved and during the course of the study;
- To be free from pressure when deciding whether to be in the study;
- To be told about new information learned during the study that might affect participants' safety or willingness to continue to take part in the study;
- To refuse to be in the study, or to change their minds about being in the study after it has started.
- To not have their care (or the care of their family members) received at CRC affected by a decision to refuse participation or discontinue participation in a research study;
- To receive a copy of the consent form that they sign indicating their willingness to participate.

Research participants, legally authorized representatives, and family members are encouraged to ask questions about the research, and to feel comfortable and confident that participating in the research is the right decision.

### **13.3 Questions, Complaints or Concerns**

From time to time, research participants, family members, employees and community members may have questions, concerns or complaints about research (including new, ongoing, or previously conducted research)



conducted on the CRC or by CRC Investigators. The following individuals may be contacted to discuss these issues in a confidential manner:

- IRB Director
- IRB Chair
- Associate Vice President, Research Compliance
- Executive Director, Research Compliance
- [BU Ethics and Compliance Hotline](#)

The above-listed individuals may take down the caller's name and contact information, or if the caller does not wish to be identified, notes will be taken on the incident or issue, and follow-up will occur with the Investigator. Depending on the nature of the call, the callers may be advised to contact the Investigator or their research personnel directly, or the individual above may act as a liaison between the two parties.

#### **13.4 Research Resources for Prospective, Current Research Participants and Family Members**

Research participants and family members are encouraged to use resources to learn more about research. The following resources may be helpful, but there are many more resources available online:

- [Connecting Community to Research](#)
- [Harvard Catalyst Research Participant Resources](#)
- [Clinical Trials.gov](#)
- [Community Connect to Research Facebook Group](#)