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Brown University Human Research Protection Program Policy and Procedure Manual

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Version - 12/2011

1 Human Research Protection Program (HRPP)

1.1 Mission:

Brown University fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the University. In the review and conduct of research, actions by the University will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (often referred to as the [Belmont Report](#)). The actions of the University will also conform to all applicable federal, state, and local laws and regulations.

In order to fulfill this mission, the University has established a Human Research Protection Program (HRPP). The mission of the HRPP is to:

- safeguard and promote the health and welfare of human research participants by ensuring that their rights, safety, and well-being are protected;
- provide timely and high quality education, review and monitoring of human research projects; and
- facilitate excellence in human research.

The HRPP includes mechanisms to:

- Establish a formal process to monitor, evaluate and continually improve the protection of human participants
- Dedicate resources sufficient to do so
- Exercise oversight of research protection
- Educate investigators and research staff about their ethical responsibility to protect research participants
- When appropriate, intervene in research and respond directly to concerns of research participants

1.2 Policy

This Human Research Protection Program (HRPP) Policy is provided in an effort to give, to the members of the research community at Brown University, comprehensive information about the organization and focus of the HRPP.

Brown University has established an Institutional Review Board (IRB) to ensure the protection of participants in human research conducted under the auspices of the University. Human research not eligible for exemption, conducted under the auspices of the University, is reviewed and approved by the Brown University IRB prior to the initiation of the research. This review is based upon Department of Health and Human

Services (DHHS) regulations, 45CFR46, and /or Federal Drug Administration (FDA) regulations, and the Belmont Report. The regulations provide a systematic means, based on established ethical principles, for protecting the rights and welfare of individuals who volunteer for Brown University research.

The IRB applies the ethical principles described in the Belmont Report and other international codes of ethics such as the Declaration of Helsinki to the conduct of human research conducted under the auspices of the University to ensure the ethically appropriate protection of research participants.

Researchers at Brown University will adhere to the standard operating procedures, for the conduct and review of all human research, found in the “Brown University Human Research Protection Program Policy and Procedure Manual.”

The following standard operating procedures (SOP) describe the authority, role, and procedures of the Brown University HRPP and IRB.

1.3 Institutional Authority

The Brown University Human Research Protection Program operates under the authority of the university policy “Human Research Protection Program (HRPP)” (section 1.2 – “Policy” above.) As stated in that policy, the operating procedures in this document serve as the governing procedures for the conduct and review of all human research conducted under the auspices of Brown University. The HRPP Policy and these operating procedures are made available to all Brown University investigators and research staff and are posted on the Research Protections Office (RPO) website.

1.4 Definitions

Human participant. A human participant is a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information (45 CFR 46.102(f)). The definition provided in the Common Rule includes investigators, technicians, and others assisting investigators, when they serve in a “participant” role by being observed, manipulated, or sampled. As required by 45 CFR 46.102(f) an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes.

For research covered by FDA regulations (21 CFR 50 and 56), human participant means an individual who is or becomes a participant in a clinical investigation (as defined below), either as a recipient of the test article or as a control. A participant may be in normal health or may have a medical condition or disease. In the case of a medical device, a human subject/participant also means any individual on whose tissue specimen an investigational device is used or tested.

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Research. Research is defined as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question. The Common Rule (45 CFR 46) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge.

Under FDA regulations, the terms *research* and *clinical investigation* are deemed to be synonymous. For the purpose of this document, the term *research* includes clinical investigations as defined below.

Clinical investigation. A clinical investigation is defined as any experiment that involves a test article and one or more human participants and that, either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act; but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding non-clinical laboratory studies. An experiment, as defined in 21 CFR 312, includes any use of a drug other than the use of a marketed (approved) drug in the course of medical practice.

Test article. A test article is a drug, device, or other article including a biological product used in clinical investigations involving human participants or their specimens.

Institutional Review Board (IRB). An IRB is a board established in accordance with, and for the purposes expressed in, the Common Rule [45 CFR 46.102(g).]

Institutional Official (IO). The President of Brown University has designated the Vice President for Research as the Institutional Official for carrying out the University's human research protections program. The IO is the Brown University official responsible for ensuring that the HRPP has the resources and support necessary to comply with all federal regulations and guidelines that govern human research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the point of contact for correspondence addressing human research with OHRP, FDA, and other federal regulatory agencies.

Research under the auspices of the University. Research under the auspices of the institution is research conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities.

Protocol. The research protocol includes the complete packet of materials submitted to the IRB for review, including a description of the research design and methodology as well as a complete description of the procedures for the protection of human participants in the research.

1.5 Ethical Principles

Brown University is committed to conducting research with the highest regard for the welfare of human participants. It upholds, and adheres to, the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). These principles are:

- 1) Respect for Persons, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
- 2) Beneficence, which is assured by ensuring that possible benefits are maximized and possible risks are minimized to all participants.
- 3) Justice, the equitable selection of participants.

The Brown University HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human participants in research conducted under its auspices.

1.6 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law, and institutional policies. All human research at Brown University is conducted in accordance with the policy and regulations found in 45 CFR 46 and 21 CFR 50 and 56. The actions of Brown University will also conform to all other applicable federal, state, and local laws and regulations.

1.7 Federalwide Assurance (FWA)

The HRPP operates under the authority of its current Federalwide Assurance (FWA00004460) and provides support to an independent Institutional Review Board (IRB), which reviews all human research protocols.

1.8 Institutional Official

The ultimate responsibility of the HRPP resides with the Vice President for Research (VPR), who serves as the Institutional Official (IO) of the program. The IO is responsible for ensuring the Brown University HRPP has the resources and support necessary to comply with all institutional policies and with federal regulations and guidelines that govern human research. The IO is legally authorized to represent Brown University. He/she is the signatory of the FWA and assumes the obligations of the FWA. The IO is the point of contact for correspondence addressing human research

with the DHHS Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), and any other federal regulatory agencies.

The IO also holds ultimate responsibility for oversight of the Institutional Review Board (IRB) and all Brown University investigators; for assuring the IRB members are appropriately knowledgeable in accordance with ethical standards and applicable regulations; for assuring the investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and for the development and implementation of an educational plan for IRB members, staff, and investigators.

1.9 Written policies and procedures

The Brown University Human Research Protection Program Policy and Procedure Manual details the policies and regulations governing research with human participants and the requirements for submitting research protocols for review by the Brown University IRB.

The policies and procedures manual is not a static document. The policies and procedures are reviewed regularly and revised by the Director of the HRPP, the Institutional Review Board, and University counsel, as necessary. The Vice President for Research will approve all revisions of the policies and procedures.

The Research Protections Office (RPO) will keep the University research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures will be available on the Brown University IRB website and copies will be available upon request.

1.10 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human participants in research. It consists of various individuals and committees such as: the Vice President for Research, the Associate Vice President for Research, the Research Protections Office, the IRB, other committees or subcommittees addressing human research protection (e.g., Biosafety, Radiation Safety, Conflict of Interest), investigators, research staff, and health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer.) The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human participants in research.

The following officials, administrative units, and individuals have primary responsibilities for implementing the HRPP:

1.10.1 Vice President for Research

As detailed above (*Institutional Official of the HRPP*), the ultimate responsibility of the HRPP resides with the Vice President for Research, who serves as the Institutional Official (IO) of the program. The responsibility for the HRPP at Brown University is delegated by the IO to the Director of the HRPP.

1.10.2 Director of the HRPP

The Director of the HRPP (RPO Director) reports to the Associate Vice President for Research and is responsible for:

1. Developing, managing, and evaluating policies and procedures that ensure compliance with all state and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the HRPP program.
2. Advising the VPR on key matters regarding research at Brown University.
3. Implementing the institution's HRPP policy.
4. Submitting, implementing, and maintaining an approved FWA through the Vice President for Research and the Department of Health and Human Services Office for Human Research Protection (OHRP).
5. Managing the finances of the Brown University HRPP.
6. Assisting investigators in their efforts to carry out the University's research mission.
7. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
8. Developing training requirements as required and as appropriate for investigators, committee members, and research staff, and ensuring that training is completed on a timely basis.

1.10.3 Institutional Review Board (IRB)

Brown University has one IRB, appointed by the Vice President for Research. The IRB prospectively reviews and makes decisions concerning all human research conducted by its employees or agents. The IRB discharges its duty by complying with the requirements of the Common Rule, state regulations, the FWA, and institutional policies. (See Section 2 for a detailed discussion of the IRB.)

1.10.4 University Counsel's Office

The Brown University HRPP relies on the University Office of General Counsel for interpretations and applications of Rhode Island law and the laws of any other jurisdiction where research is conducted as they apply to human research.

1.10.5 The Investigator

The investigator is the ultimate protector of the individuals who participate in research. The investigator is expected to abide by the highest ethical standards and for developing a protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process. The investigator must establish and maintain an open line of communication with all research participants within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff completes appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the investigator is responsible for providing written procedures for their storage, security, dispensing, and disposal that may be coordinated through the appropriate pharmacist.

1.10.6 Relationship between Components

The IRB functions independently of, but in coordination with, other institutional regulatory committees. The IRB, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human participants are adequately protected. The IRB has review jurisdiction over all research involving human participants conducted, supported, or otherwise subject to regulation, by any federal department or agency that has adopted the human research regulations.

The Research Compliance Network will meet to ensure a dialogue is maintained between the various compliance entities at the University. With the Associate Vice President for Research as chair, the committee will act in an advisory capacity to the Vice President for Research, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has been disapproved by the IRB.

1.11 HRPP Operations

In addition to the leadership structure described previously, other support staff members for the HRPP may include coordinators, managers, administrative support staff, and the RPO assistant director.

1.11.1 HRPP Office

The Brown University HRPP office, known as the Research Protections Office (RPO), reports directly to the Associate VPR and is supervised by the Director of RPO (Director). The Director has expert knowledge in regulatory issues regarding human research protections, serves as the Human Protections Administrator, and is the primary contact at Brown University for the Office for Human Research Protections, Department of Health and Human Services.

The Director of RPO has day-to-day responsibilities for the operation of the IRB. This includes responding to faculty, student, and staff questions about human research as well as organizing and documenting the review process. The Director works closely with the Chair of the IRB in the development of policy and procedures and is a voting member of the IRB. Additionally, the office is staffed by an assistant director, managers, coordinators, and a program support assistant. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis.

1.11.2 IRB Manager

The IRB Manager is responsible for all aspects of the IRB throughout the review process of a research protocol involving human participants. This responsibility includes the initial review of documents and screening of research protocols prior to its review by the IRB, as well as serving as the liaison between the investigators and the IRB. The IRB Manager reviews the IRB minutes for accuracy and ensures proper documentation of discussions including controverted discussions and actions taken by IRB during convened meetings.

1.11.3 IRB Coordinator

The IRB Coordinator is responsible for providing administrative and clerical support to the IRB Chair and IRB managers as well as scheduling and coordinating all IRB functions. The IRB Coordinator is also responsible for IRB record retention. The IRB Coordinator is responsible for maintaining complete IRB files, including records of all research protocols, IRB correspondence (including e-mails), and research credentialing file records of investigators.

1.12 HRPP Resources

RPO is equipped with all necessary office space, meeting space, storage space and equipment to perform the functions required for the HRPP. The adequacy of personnel and non-personnel resources of the HRPP program is assessed regularly by the Director with the RPO staff and are reviewed and approved by the IO.

The IO provides resources to the IRB and RPO, including adequate meeting and office space and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, scanners, and copy

machines, will be made available to the IRB and staff. The resources provided for the IRB and RPO will be reviewed during the annual budget review process.

1.12.1 Institutional Audits and Compliance Reviews

Directed (“for cause”) audits and periodic compliance reviews (“not for cause”) will be conducted to assess investigator compliance with federal, state, and local law and University policies; to identify areas for improvement; and to suggest recommendations based on existing policies and procedures. Directed audits of IRB-approved research studies are in response to identified concerns. Periodic (“not for cause”) compliance reviews are conducted using a systematic method to review IRB-approved research on a regular basis. The results will be reported to the Director and the IRB Chair.

Activities of auditors during directed audits and periodic compliance reviews may include:

- a) requesting progress reports from researchers;
- b) examining investigator-held research records;
- c) contacting research participants;
- d) observing research sites where research involving human research participants and/or the informed consent process is being conducted;
- e) auditing advertisements and other recruiting materials as deemed appropriate by the IRB;
- f) reviewing projects to verify from sources other than the researcher that no unapproved changes have occurred since the previous review;
- g) monitoring conflict of interest concerns to assure the consent documents include the appropriate information and disclosures;
- h) conducting other monitoring or auditing activities as deemed appropriate by the IRB.

1.12.2 Non-University Institutional Audits and Compliance Reviews

External directed (“for cause”) audits and compliance reviews may be conducted at non-University sites, where the University’s IRB serves as the “IRB of Record” to assess compliance with federal, state, and local law; participant safety; and IRB policies and procedures. These directed audits are implemented in response to identified concerns that require an IRB determination. These reviews may include items listed in Section 1.12.1 above.

1.12.3 Reporting and Disposition

The results are reported to the Director and the IRB Chair. Any noncompliance will be handled according to the procedures in Section 9 of this manual.

If an audit or review finds that participants in a research project have been exposed to unexpected serious harm, such findings will be promptly reported to the Director and the IRB Chair for immediate action.

1.12.4 IRB Internal Compliance Reviews

Internal directed audits and random internal compliance reviews may be conducted. The results may impact current practices and may require additional educational activities, and will be reported to the Director. The RPO staff will:

- a) review the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as other risk/benefit ratio and consent issues that are included in the criteria for approval;
- b) assess the IRB minutes to assure that quorum was met and maintained;
- c) assess the current adverse event reporting process;
- d) assess that privacy provisions, as needed, have been adequately reviewed, discussed, and documented in the IRB minutes;
- e) evaluate the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
- f) observe IRB meetings or other related activities;
- g) review IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
- h) review the IRB database to assure all fields are completed accurately;
- i) verification of IRB approvals for collaborating institutions or external performance sites, as necessary; and
- j) other monitoring or auditing activities deemed appropriate by the IRB.

1.12.5 IRB Internal Quality Improvement

The Director will review the results of internal compliance reviews with the IRB Chair and the IO. If any deficiencies are noted in the review, a corrective action plan will be developed by the Director and approved by the IO. The Director will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the IO.

1.13 Collaborative Research Projects

In the conduct of cooperative research projects, Brown University acknowledges that each institution is responsible for safeguarding the rights and welfare of research participants and for complying with applicable federal regulations. When a cooperative agreement exists, Brown University may enter into a joint review arrangement, rely on the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort. A formal relationship must be established between the University and the other institution through either a Cooperative Agreement, a Memorandum of Understanding, or an IRB Authorization Agreement (IAA). This relationship must be formalized before the University will accept any human research proposals from the other institution or rely on the review of the other institution.

For collaborative research, the PI must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of protocol information (IRB initial and continuing approvals, relevant reports of unanticipated problems, protocol modifications, and interim reports) between all participating institutions.

- When Brown University relies on another IRB, the RPO staff will ensure that the other organization has an active Assurance and appropriate policies in place.
- When Brown University reviews research conducted at another institution, the particular characteristics of each institution's local research context must be considered, either (i) through knowledge of its local research context by the Brown University IRB or (ii) through subsequent review by appropriate designated institutional officials, such as the Chairperson and/or other IRB members.

The investigator is responsible for serving as the single liaison with outside regulatory agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The investigator is responsible for ensuring that the research study is reviewed and approved by any other appropriate committees at the collaborating facility and at the participating facilities prior to enrollment of participants.

2 Institutional Review Board

2.1 Purpose

The following describes the authority, role, and procedures of the Brown University Institutional Review Board (IRB). The IRB is established to ensure the protection of human participants in research under the auspices of Brown University.

2.2 IRB Authority

Under University policy “Human Research Protection Program (HRPP),” the IRB is authorized to:

1. approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of Brown University;
2. suspend or terminate approval of research not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to participants;
3. observe, or have a third party observe, the consent process; and
4. observe, or have a third party observe, the conduct of the research.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the institution. However, those officials may NOT approve research if it has been disapproved by the IRB. University officials may strengthen requirements and/or conditions, or add other modifications to secure University approval or approval by another University committee. Previously approved research protocols and/or consent forms must be re-approved by the IRB before initiating the changes or modifications. The IRB Chair or RPO Director makes the determination whether the changes require full IRB re-review or expedited review.

2.3 Number of IRBs

There is currently one institution-wide Institutional Review Board. The IO, the RPO Director, and the Chair of the IRB will review the activity of the IRB on at least an annual basis and make a determination as to the appropriate number of IRBs that are needed for the institution.

2.4 Roles and Responsibilities

2.4.1 Chairperson of the IRB

The Brown University IO (Vice President for Research), in consultation with the IRB members and the RPO Director, appoints a Chair and Vice Chair of the IRB. Any change in appointment, including reappointment or removal, requires written notification. Appointments may, or may not, have a specified term.

The IRB Chair should be a highly respected individual, from within the University, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial, and immune to pressure by the institution's administration, the investigators whose protocols are brought before it, and other professional and nonprofessional sources.

The IRB Chair is responsible for conducting the meetings and is a signatory for correspondence generated by the IRB, as is the Associate Vice President for Research, the Vice-Chair, and RPO Director.

The IRB Chair may designate other IRB members to perform duties, as appropriate, for review, signature authority, and other IRB functions, e.g., the Vice Chair and RPO Director.

The IRB Chair advises the IO and RPO Director about IRB member performance and competence.

The performance of the IRB Chair will be reviewed on an annual basis by the RPO Director in consultation with the IO. If the Chair is not acting in accordance with the IRB's mission, not following these policies and procedures, has an undue number of absences, or is not fulfilling the responsibilities of the Chair, he/she will be removed.

2.4.2 Vice Chair of the IRB

The Vice Chair serves as the Chair of the IRB in the absence of the Chair and has the same qualifications, authority, and duties as Chair.

2.4.3 Subcommittees of the IRB

The Chair, in consultation with the RPO Director, may designate one or more other IRB members, i.e. a subcommittee, to perform duties, as appropriate, for review, signature authority, and other IRB functions.

Duties of a subcommittee may include the following:

1. serve as designees by the IRB Chair for the expedited review of new or continuing protocols, and/or modifications of continuing protocols. The subcommittee must be experienced in terms of seniority on the IRB.
2. review and approve the revisions requiring only simple concurrence submitted by investigators for a protocol given provisional approval by the convened IRB.
3. conduct an inquiry. A subcommittee is appointed consisting of IRB members, and non-members, if appropriate, to conduct an inquiry into allegations of non-compliance. The subcommittee is given a charge by the IRB, which can include any or all of the following:
 - a. review of protocol(s) in question;

- b. review of audit reports of the investigator, if appropriate;
 - c. review of any relevant documentation, including consent documents, case report forms, participants' files, as they relate to the investigator's execution of her/his study involving human participants;
 - d. interview of appropriate personnel, if necessary;
 - e. preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting;
 - f. recommend actions, if appropriate.
4. Conduct on-site review. Determination is made by the IRB on a protocol-by-protocol basis of the review interval and the need for additional supervision and/or participation. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by an IRB subcommittee might occur or approval might be subject to an audit of study performance after a few months of enrollment or after enrollment of the first several participants.

2.5 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, specific community concerns in addition to representation by multiple, diverse professions, knowledge and experience with vulnerable participants, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompass most of the research performed at Brown University. The University has procedures (See Section 4) that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

In addition, the IRB will include members who are knowledgeable about, and experienced working with, vulnerable populations that typically participate in Brown University research or have ready access to consultants with appropriate knowledge and experience.

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of research participants and possess the professional competence necessary to review specific research activities. A member of the IRB may fill multiple membership position requirements for the IRB.

2.6 Composition of the IRB

1. The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
2. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of 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 participants.

3. In addition to possessing the professional competence necessary to review specific research activities, the IRB will be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice.
4. If the IRB regularly reviews research that involves a vulnerable category of participants (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these participants. When protocols involve vulnerable populations, the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the IRB or as consultants.
5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. The IRB shall not consist entirely of members of one profession.
6. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
7. The IRB includes 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.
8. One member may satisfy more than one membership category.
9. The RPO Director and administrators may be voting members of the IRB.

2.7 Appointment of Members to the IRB

The IRB Chair, Vice Chair, and/or the RPO Director, identifies a need for a new or replacement member, or alternate member. The IRB may nominate candidates and send the names of the nominees to RPO. Department Chairs and others may forward nominations to the IO, to RPO, or to an IRB Chair or Vice-Chair.

For faculty members, the RPO Director, contacts the nominee. If there are no nominees, then appropriate Department Chairs or Program Directors will be contacted concerning the vacancies and to solicit nominees.

The final decision in selecting a new member is made by the IO, the IRB Chair, and the RPO Director.

Appointments may, or may not, have a specified term. Any change in appointment, including reappointment or removal, will be provided through written notification. Members may resign by written notification to the Chair or the RPO Director.

At appropriate intervals, the IRB Chair and the RPO Director review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

2.8 Alternate members

The appointment and function of alternate members is the same as that for primary IRB members, and the alternate's expertise and perspective are comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) for whom each alternate member may substitute. The IRB minutes will document when an alternate member replaces a primary member. If both primary and alternate members are present at the meeting, it will be made clear at the outset which member is there in a voting capacity.

2.9 Use of Consultants (Outside Reviewers)

When necessary, the IRB Chair or the RPO Director may solicit individuals from the University or the community with competence in special areas to assist in the review of issues or protocols which require appropriate expertise beyond or in addition to that available on the IRB. The need for an outside reviewer is determined in advance of the meeting by the Director or the Chair by reviewing the protocols scheduled to be reviewed at the convened meeting. RPO will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Key information provided by consultants at meetings will be documented in the minutes. Written reviews provided by the outside reviewer, as necessary, will be filed with the protocol.

The RPO staff reviews the conflicting interest policy for IRB members (7.5.3) with consultants, and consultants must verbally confirm to the RPO Director that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or family members have a conflicting interest in the sponsor of the research will not be invited to provide consultation.

The consultant's findings will be presented to the full board for consideration either in person or in writing. If in attendance, these individuals will provide consultation but may not participate in or observe the vote.

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

2.10 Duties of IRB Members

The agenda, submission materials, protocols, proposed informed consent forms and other appropriate documents are distributed to members prior to the convened meetings at which the research is scheduled to be discussed. In general, members receive the materials for review at least one week before each meeting, in order to participate fully in the review of each proposed project. IRB members will treat the research proposals, protocols, and supporting data confidentially. All copies of the protocols and supporting data are returned to the IRB staff at the conclusion of the review for professional document destruction.

2.11 Attendance Requirements

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Chair, Vice Chair, or an RPO staff member. If the inability to attend will be prolonged, a request for an alternate to be assigned may be submitted to the Chair or the Director.

If an IRB member is to be absent for an extended period of time, such as for a sabbatical, it is anticipated that he or she will notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained, if necessary. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the IRB. If the member has a designated alternate, the alternate can serve during the primary member's absence.

2.12 Training / Ongoing Education of Chair and IRB Members in Regulations, Procedures

A vital component of a comprehensive human research protection program is an education program for IRB Chair and the IRB members. Brown University is committed to providing training and an on-going educational process for IRB members and the staff of RPO, related to ethical concerns and regulatory and institutional requirements for the protection of research participants.

Orientation

New IRB members, including alternate members will meet with the IRB Chair and RPO Director for an informal orientation session. At the session, the new member will be given materials that include:

- Belmont Report;

- Brown University HRPP Policy and Procedures Manual;
- Federal regulations relevant to the IRB

New members are required to complete the initial education requirement for IRB members before they may serve as Primary Reviewer.

Initial Education

IRB members will complete the following web based training:

- Brown University CITI program; and the
- IRB Member Module - "What Every New IRB Member Needs to Know" at the CITI site.

Continuing Education

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB. Educational activities may include, but are not limited to;

- in-service training at IRB meetings;
- training workshops and special issues meetings;
- copies of appropriate publications;
- identification and dissemination by the RPO Director of new information that might have affected the HRPP, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings.

The RPO staff is required to complete the Brown University CITI program. Staff will attend PRIMR or OHRP training, whenever possible.

RPO staff is encouraged to seek certification in areas of expertise, such as Certified IRB Professional (CIP).

2.13 Review of IRB Member Performance

The IRB members' performance will be reviewed at regular intervals by the RPO Director. Members who are not acting in accordance with the IRB's mission or policies and procedures or who have an undue number of absences will be removed.

2.14 Reporting and Investigation of Allegations of Undue Influence

If an IRB chair, member, or staff person feels that the IRB has been unduly influenced by any party, they shall make a confidential report to the IO and/or President, depending on the circumstances. The official receiving the report will conduct a thorough investigation and corrective action will be taken to prevent additional occurrences.

3 IRB Review Process

3.1 Purpose

The following describe the procedures required for the review of research by the IRB.

3.2 Definitions

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

Minor change. A minor change is one which, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. the level of risks to participants
2. the research design or methodology (adding procedures that are not eligible for expedited review [See Section 3.5] would not be considered a minor change)
3. the qualifications of the research team
4. the facilities available to support safe conduct of the research
5. any other factor which would warrant review of the proposed changes by the convened IRB.

Quorum. A quorum of the IRB consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

Suspension of IRB approval. A suspension is a directive of the convened IRB or other authorized individual (See Section 3.10) to temporarily stop short some or all previously approved research activities. Suspended protocols remain open and require continuing review.

Termination of IRB approval. A directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

3.3 Human Research Determination

The responsibility for initial determination as to whether an activity constitutes human research rests with the investigator. The investigator should make this determination based on the definitions of “human participant” and “research” in Section 1.4. Since the University will hold them responsible if the determination is not correct, investigators may request a confirmation that an activity does not constitute human research from RPO. The request may be made verbally, by phone contact, by email, or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination.

Determinations as to whether an activity constitutes human research will be made according to the definitions in Section 1.4. Determinations regarding activities that either clearly are, or clearly are not, human research, may be made by the IRB Manager. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

3.4 Exempt Studies

All research using human participants must be approved by the institution. Certain categories of research (i.e., “exempt research”) do not require convened IRB review and approval. Exempt research is subject to institutional review and must be determined by the IRB Chair, Vice Chair, or the Director of RPO or designee.

The exemption is good for three years. If the research extends beyond that date, the researcher has to request another exemption.

3.4.1 Limitations on Research Participants

Vulnerable Populations:

- Children: Exemptions for research do not apply, *except* for use of exempt category (4)[see 46.101(b)(4)] for secondary data analysis of data about children.
- Children: All research involving an interaction or intervention with children requires full board review.
- Prisoners: exemptions do NOT apply. IRB review is required.

3.4.2 Categories of Exempt Research

With the above exceptions, research activities not regulated by the FDA (see Section 3.4.3 for FDA Exemptions) in which the only involvement of human participants will be in one or more of the following categories are exempt from IRB review, but require institutional review and determination:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - a) research on regular and special education instructional strategies, or
 - b) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - a) information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and
 - b) any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participant's financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
 - a) the human participants are elected or appointed public officials or candidates for public office; or
 - b) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants. NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
5. Research and demonstration projects which are conducted by or subject to the approval of federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
 - a) Public benefit or service programs;
 - b) Procedures for obtaining benefits or services under those programs;
 - c) Possible changes in or alternatives to those programs or procedures; or
 - d) Possible changes in methods or levels of payment for benefits or services under those programs.

Such projects must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements for IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of participants, and the exemption must be invoked only with authorization or concurrence by the funding agency.

6. Taste and food quality evaluation and consumer acceptance studies,
 - a) If wholesome foods without additives are consumed; or
 - b) 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.

3.4.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of IRB review:

1. 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. [21 CFR 56.104(c)]
2. 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. [21 CFR 56.104(d)]

3.4.4 Additional Protections

Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for participants in keeping with the guidelines of the Belmont Report.

3.4.5 Exemption Request Procedures

Investigators must submit “IRB Form #1” including, but not limited to, the following documentation:

1. a summary of the research
2. a description of the research procedures
3. consent documents
4. plan for privacy and confidentiality
5. plan for dissemination of findings
6. a copy of the proposal if the research is externally funded
7. expected date of completion

The application must be signed and dated by the responsible Principal Investigator.

Investigators will be given feedback either by phone or email as to the qualification of the application for exempt status. Once institutional review is completed, IRB staff will send an email and paper notification to the PI of the results of the review.

3.5 Expedited Review

An IRB may use the expedited review procedure to review either or both of the following:

1. some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk,
2. minor changes in previously approved research during the period (of one year or less) for which approval is authorized

At Brown University expedited categories of review cannot be used for the initial review of research involving children, *except* for use of expedited category (5) for secondary data analysis of data about children. Initial review of all research involving an interaction or intervention with children requires full board review.

3.5.1 Categories of Research Eligible for Expedited Review

[63 FR 60364-60367, November 9, 1998]

The activities listed below 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 participants.

- The categories in this list apply regardless of the age of participants, except as noted.
- The expedited review procedure may not be used where identification of the participants and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the participants 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.
- The expedited review procedure may not be used for classified research involving human participants.
- 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.

Research 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 participants, 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 children¹, considering the age, weight, and health of the participants, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these participants, 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. [¹Children are defined in the DHHS regulations as "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."][45
[CFR 46.402\(a\)](#)]

(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 gum base 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 participant or an invasion of the participant'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). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

(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. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

- (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 participants; (ii) all participants have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of participants;
or
 - (b) where no participants have been enrolled and no additional risks have been identified; *or*
 - (c) where the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no participants have been enrolled" is interpreted to mean that no participants have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

- (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.

[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (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. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.]

3.5.2 Expedited Review Procedures

Investigators must submit "IRB Form #1" including, but not limited to, the following documentation:

1. a summary of the research;
2. a description of the research procedures

3. consent documents
4. plan for privacy and confidentiality
5. plan for dissemination of findings
6. a copy of the proposal if the research is externally funded.
7. expected date of completion.

The application must be signed and dated by the responsible Principal Investigator.

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB.

The designees must be experienced (having served on the IRB for at least one year) voting members of the IRB. Selected reviewers will be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see Section 3.6.9) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), should receive and review all documentation that would normally be submitted for a full-board review including the complete protocol, a progress report form summarizing the research since the previous review (including adverse events), notes from the pre-screening conducted by the RPO staff, the current consent documentation and determine the regulatory criteria for use of such a review procedure.

The reviewer(s) conducting initial or continuing review determine whether the research meets the criteria allowing review using the expedited procedure and if so, whether the research meets the regulatory criteria for approval. If the research does not meet the criteria for expedited review, the reviewer will indicate that the research requires full review by the IRB; and the protocol will be placed on the agenda for an upcoming IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 3.8 & 3.9 and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth below.

Reviewers will indicate approval, required modifications, or disapproval in writing, i.e. via email. If modifications are required, RPO staff will inform the investigator by e-mail. If the modifications are minor, the RPO staff may determine if the investigator has sufficiently addressed the modifications. If the modifications are major, or if the reviewer(s) request it, the modified protocol will be sent back to the IRB member(s) for further review.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the RPO Director and/or IRB Chair may make a final

determination. Upon the discretion of the RPO Director or IRB Chair, the protocol will be submitted to the IRB for review.

3.5.3 Informing the IRB

IRB members will be apprised of all expedited review approvals by means of a list in the meeting agenda. Any IRB member can request to review the full protocol by contacting RPO.

3.6 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all research at convened meetings at which a quorum of the members is present.

3.6.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings be found on the RPO website. Special meetings may be called at anytime by the Chair or the Director.

3.6.2 Preliminary Review

Investigators must submit “IRB Form #1” including, but not limited to, the following documentation:

1. a summary of the research;
2. a description of the research procedures
3. consent documents
4. plan for privacy and confidentiality
5. plan for dissemination of findings
6. a copy of the proposal if the research is externally funded.
7. expected date of completion.

RPO staff will perform a preliminary review of all protocol materials submitted for determination of completeness and accuracy. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by e-mail, phone, or in person of missing materials and the necessary date of receipt for inclusion on that month’s agenda. In the case of a PI who is submitting a protocol for the first time or an investigator who may not be well-versed in the protocol submission procedures, individualized IRB consultations can be arranged. Specific questions about the IRB policies and procedures, assistance with the determination of whether a particular protocol is human research or not and what particular forms are required can be submitted to RPO staff for information and/or clarification. Individual appointments with RPO staff can also be arranged and are strongly recommended for first-time submissions.

3.6.3 Primary and Secondary Reviewers

After it has been determined that the protocol submission is complete, RPO staff, with the assistance of the IRB Chair, as necessary, will assign protocols for review paying close attention to the scientific content of the protocol and the potential reviewer's area of expertise. At least one reviewer will be assigned to each protocol and a reviewer may be assigned several protocols or other research items for review. Reviewers are assigned to all protocols requiring initial review and to all modifications. When the IRB is presented with a protocol which may be outside of the knowledge base of any of the IRB members, an outside consultant will be sought.

The primary reviewers are responsible for:

1. having a thorough knowledge of all of the details of the proposed research.
2. performing an in-depth review of the proposed research.
3. leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and leading the IRB through the regulatory criteria for approval (See Section 3.8).
4. making suggestions for changes to the proposed research, where applicable.

If the primary reviewer is absent from the meeting, a new reviewer may be assigned, providing the new reviewer has reviewed the materials prior to the meeting.

Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary reviewer. It should be noted that IRB members receive, and are expected to review, the entire protocol package for all studies, not just the ones to which they are assigned as reviewers.

3.6.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted (in full) by the last day of the month in order to be included on the IRB agenda of the following month. Deadline dates can vary occasionally, and the RPO web page should be checked for the latest information.

The meeting agenda will be distributed to the IRB members prior to the meeting. The agenda packet includes the IRB agenda, prior month's meeting minutes, applicable business items, appropriate continuing education materials, and protocol review materials. IRB members receive their review materials one week before the scheduled meeting, whenever possible, to allow sufficient time for the review process.

3.6.5 Materials received by the IRB

Each IRB member receives the following documentation, as applicable:

1. complete protocol application form
2. project description (complete protocol description)
3. proposed consent /parental permission /assent form(s)
4. recruitment materials /participant information
5. data collection documents (including surveys and questionnaires)

6. other related documents, as necessary

At least one reviewer must receive and review: relevant grant applications; the sponsor's protocol (when one exists); the investigator's brochure (when one exists); the DHHS-approved sample informed consent document (when one exists); the complete DHHS-approved protocol (when one exists).

Any IRB member may request any of the material provided to the primary and secondary reviewers by contacting RPO.

If an IRB member requires additional information to complete the review, they may contact the investigator directly or RPO to make the request of the investigator.

3.6.6 Quorum

A quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate quorum is present before calling the meeting to order. The IRB Chair will be responsible to ensure that the meetings remain appropriately convened.

A quorum must be maintained for each vote to occur. RPO staff takes note of arrivals and departures of all members and notifies the chair if a quorum is not present. If a quorum is not maintained, the protocol must be deferred or the meeting must be terminated.

Members are considered present and counted towards the quorum if participating through teleconferencing or videoconferencing. In this case the member must have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

3.6.7 Meeting Procedures

The IRB Chair, or Vice Chair in the event that the IRB Chair is absent, will call the meeting to order, once it has been determined that a quorum is in place. The Chair or Vice Chair will remind IRB members to recuse themselves from the discussion and vote by leaving the room where there is a conflict. The IRB will review and discuss the IRB minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting, if requested by the IRB.

The IRB reviews all submissions for initial and continuing review, as well as requests for amendments. The reviewer(s) presents an overview of the research and leads the IRB through the completion of the regulatory criteria. All members present at a convened meeting have full voting rights, except in the case of a conflict of interest. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the RPO staff to record the proceedings of the session and to take minutes at each IRB meeting.

3.6.8 Guests

At the discretion of the IRB, the PI may be invited to the IRB meeting to answer questions about their proposed or ongoing research. The PI may not be present for the discussion or vote on their research.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the RPO Director. Guests may not speak unless requested by the IRB and may be required to sign a confidentiality agreement.

3.6.9 IRB Member Conflicts of Interest

IRB members and consultants will not participate in any IRB action taken, including the initial and continuing review of any project, in which the member has a conflicting interest, except to provide information requested by the IRB. IRB members are expected to self-identify conflicting interests. A full board reviewer or expedited reviewer with a conflict of interest must notify the RPO staff who will re-assign the protocol. Roles that would present a conflict of interest include, but are not limited to, principal investigator, co-investigator, and graduate student advisor.

Except when requested by the IRB to be present to provide information, IRB members will absent themselves from the meeting room when the IRB reviews research in which they have a conflicting interest. The Chair will allow for board discussion once the conflicted member has recused him/herself. The absent member is not counted toward quorum and his/her absence during the discussion and vote on the protocol will be noted in the IRB meeting minutes.

If the conflict of interest status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair and/or RPO Director.

3.7 Criteria for IRB Approval of Research

In order for the IRB to approve human research, it must determine that the following requirements are satisfied:

(1) Risks to participants are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk, and (ii) whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

(2) Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, 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 participants 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 participants 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 involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants.

(7) When appropriate, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

(8) When some or all of the participants are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these participants.

3.7.1 Risk/Benefit Assessment

The goal of the assessment is to ensure that the risks to research participants posed by participation in the research are justified by the anticipated benefits to the participants or society. Toward that end, the IRB must:

1. judge whether the anticipated benefit, either of new knowledge or of improved health for the research participants, justifies asking any person to undertake the risks;
2. disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research - one of the major responsibilities of the IRB - involves a series of steps:

1. identify the risks associated with the research, as distinguished from other risks, such as the risks of therapies the participants would receive even if not participating in research;
2. determine whether the risks will be minimized to the extent possible;
3. identify the probable benefits to be derived from the research;
4. determine whether the risks are reasonable in relation to the benefits to participants, if any, and assess the importance of the knowledge to be gained;
5. ensure that potential participants will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;

Risks to participants are minimized:

1. by using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk; and
2. whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

Risks to participants are reasonable in relation to anticipated benefits, if any, and to the importance of the knowledge that may reasonably be expected to result.

1. 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 participants would receive even if not participating in the research.
2. The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3.7.1.1 Scientific Merit

In order to assess the risks and benefits of the proposed research, the IRB must determine that:

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question; and
- The knowledge expected to result from this research is sufficiently important to justify the risk.

In making this determination, the IRB may draw on its own knowledge and disciplinary expertise, or the IRB may draw on the knowledge and disciplinary expertise of others, such as reviews by a funding agency or departmental review.

3.7.2 Selection of participants is equitable.

The IRB determines by viewing the application, protocol, and other research project materials that the selection of participants is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of participants or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates: the purposes of the research; the setting in which the research occurs; scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; the scientific and ethical justification for excluding classes of persons who might benefit from the research; and the inclusion/exclusion criteria.

At the time of the continuing review the IRB will determine that the PI has followed the selection criteria that s/he originally set forth at the time of the initial IRB review and approval.

3.7.2.1 Recruitment of Participants

The investigator will provide the IRB with all recruiting materials to be used in identifying participants including recruitment methods, advertisements, and payment arrangements. See Section 3.8.7 for a discussion of IRB review of advertisements, Section 3.8.8 for a discussion of IRB review of payments.

3.7.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the Committee will ensure that informed consent will be appropriately documented in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. See Section 5 for detailed policies on informed consent.

3.7.4 Data Safety Monitoring

The IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of participants. For research in which risks are substantial, the IRB may require a general description of the data and safety-monitoring plan to be submitted to the IRB as part of the protocol. This plan should contain procedures for reporting adverse events (AEs). In general, it is desirable for a Data and Safety Monitoring Board (DSMB) to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable participants, or

employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed, and will continue to review, study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

3.7.5 Privacy and Confidentiality

The IRB will determine whether adequate procedures are in place to *protect the privacy of participants* and to *maintain the confidentiality of the data*.

Definitions

- Privacy - having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.
- Confidentiality - methods used to ensure that information obtained by researchers about their participants is not improperly divulged.

Regulations

46.102(f) Human subject means a living individual about whom an investigator... conducting research obtains

(1) data through intervention or interaction with the individual,

or

(2) identifiable private information.

- Private information - information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- Identifiable information – information where the identity of the participant is or may readily be ascertained by the investigator or associated with the information.

Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to participants or participants' information and the participants expectations of privacy in the situation. Investigators must have appropriate authorization to access the participants or the participants' information.

Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the participants from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

At the time of initial review, the IRB ensures that the privacy and confidentiality of research participants is protected. The IRB assesses whether there are adequate provisions to protect participant privacy and maintain confidentiality. The IRB does this through the evaluation of the:

- a. methods used to obtain information about participants,
- b. methods used to obtain information about individuals who may be recruited to participate in studies
- c. the use of personally identifiable records and
- d. the methods to protect the confidentiality of research data.

In some cases, the IRB may also require that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 4.16.8). The PI will provide the information regarding the privacy and confidentiality of research participants at the time of initial review through the completion of the research protocol. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research participants is sufficiently protected.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It shall evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

3.7.6 Vulnerable Populations

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable participants in research. The IRB may determine and require that, when appropriate, additional safeguards are put into place for vulnerable participants, such as those without decision-making capacity.

The IRB carefully evaluates each protocol to determine if vulnerable participants are included in the study population and what measures have been taken to protect them.

The IRB is required to consider the scientific and ethical reasons for including vulnerable populations in research. The IRB must pay special attention to specific elements of the research plan when reviewing research involving vulnerable participants. These specific elements may include strategic issues such as inclusion and exclusion criteria for selecting and recruiting participants, informed consent and willingness to volunteer, coercion and undue influence and confidentiality of data.

The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants. For example, it is not appropriate to focus on prisoners as research participants merely because they are a readily available "captive" population.

The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

3.8 Additional Considerations during IRB Review and Approval of Research

3.8.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either “minimal” or “greater than minimal” based on the “absolute” interpretation of minimal risk. The meeting minutes will reflect the Committee’s determination regarding risk levels for full board protocols.

3.8.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols. All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required. The meeting minutes will reflect the IRB’s determination regarding review frequency.

3.8.2.1 Review More Often than Annually

Research that meets any of the following criteria may require review more often than annually:

1. significant risk to research participants (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the participants;
2. the involvement of especially vulnerable populations likely to be subject to coercion (e.g., terminally ill)
3. a history of serious or continuing non-compliance on the part of the PI.

The following factors will also be considered when determining which studies require review more frequently than on an annual basis:

1. probability and magnitude of anticipated risks to participants.
2. likely medical condition of the proposed participants.
3. overall qualifications of the PI and other members of the research team.
4. specific experience of the PI and other members of the research team in conducting similar research.

5. nature and frequency of adverse events observed in similar research at this and other institutions.
6. novelty of the research making unanticipated adverse events more likely.
7. any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of participants either studied or enrolled. If a maximum number of participants studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed 1 year and that the number of participants studied or enrolled determines the approval period only when that number of participants is studied or enrolled in less than 1 year.

3.8.3 Independent Verification that No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of participants sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, for example, in cooperative studies, or other multi-center research.

The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. protocols where concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
2. protocols conducted by PIs who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
3. protocols randomly selected for internal audit.
4. whenever else the IRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

1. probability and magnitude of anticipated risks to participants.
2. likely medical condition of the proposed participants.
3. probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments, and/or review of adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

3.8.4 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to participants, or if participants are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

See Section 5.7 for a detailed discussion of consent monitoring.

3.8.5 Investigator Conflicts of Interest

The protocol form asks protocol-specific questions regarding conflict of interest for the investigators and key personnel. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict management plan that adequately protects the human participants in the protocol is in place.

3.8.6 Significant New Findings

During the course of research, significant new knowledge or findings about the topic under study may develop. The PI must report any significant new findings to the IRB, and the IRB will review them with regard to the impact on the participants' rights and welfare. Since the new knowledge or findings may affect the risks or benefits to participants or participants' willingness to continue in the research, the IRB may require, during the ongoing review process, that the PI contact the currently enrolled participants to inform them of the new information. The IRB will communicate this to the PI. The informed consent should be updated and the IRB may require that the currently enrolled participants be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

3.8.7 Advertisements

The IRB must approve all advertisements prior to posting and/or distribution for studies that are conducted under the purview of the Brown University IRB. The IRB will review:

1. information contained in the advertisement
2. mode of communication
3. final copy of printed advertisements, when necessary
4. final audio/video taped advertisements, when necessary

This information should be submitted to the IRB with the initial application or as an amendment to the protocol.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic, creating undue influence to participate which includes but is not limited to:

1. statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol
2. using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article was investigational
3. promising “free medical treatment” when the intent was only to say participants will not be charged for taking part in the investigation
4. emphasis on payment or the amount to be paid, such as bold type or larger font on printed media
5. inclusion of exculpatory language
6. claims, either explicitly or implicitly, that the drug, biologic or device was safe or effective for the purposes under investigation and/or that the test article was known to be equivalent or superior to any other drug, biologic or device

Any advertisement to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. name and address of the investigator and/or research facility.
2. condition being studied and/or the purpose of the research.
3. criteria that will be used to determine eligibility for the study, in summary form.
4. time or other commitment required of the participants.
5. location of the research and the person or office to contact for further information.
6. clear statement that this is research and not treatment.
7. brief list of potential benefits (e.g. no cost of health exam).

3.8.8 Payment to Research Participants

Payment to research participants may be an incentive for participation or a way to reimburse a participant for travel and other experiences incurred due to participation. However, payment for participation is not considered a research benefit. Regardless of the form of remuneration, investigators must take care to avoid coercion of participants. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation. The amount of compensation must be proportional to the risks and inconveniences posed by participation in the study.

Investigators who wish to pay research participants must indicate in their research protocol the justification for such payment. Such justification should:

- a) substantiate that proposed payments are reasonable and commensurate with the expected contributions of the participant;

- b) state the terms of the participation agreement and the amount of payment in the informed consent form; and
- c). substantiate that payments are fair and appropriate and that they do not constitute (or appear to constitute) undue pressure on the participate to volunteer for the research study.

The IRB must review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence.

Credit for payment should accrue and not be contingent upon the participant completing the entire study. Whenever possible, the IRB does not allow the entire payment to be contingent upon completion of the entire study. Any amount paid as bonus for completion of the entire study should not be so great that it becomes coercive.

The consent form should describe the terms of payment and the conditions under which participants would receive partial payment or no payment (e.g., if they withdraw from the study before their participation is completed).

3.8.9 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from others (“finder’s fees”) is not permitted. Similarly payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (“bonus payments”) are also not permitted.

3.8.10 Certificates of Confidentiality (CoC)

Where research involves the collection of highly sensitive information about individually identifiable participants, the IRB may determine that special protections are needed to protect participants from the risks of investigative or judicial processes. In such situations the IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC).

For studies not funded by DHHS, if there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA. The CoC was developed to protect against the involuntary release of sensitive information about individual participants for use in federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

The IRB may determine that an investigator should request a certificate of confidentiality from the National Institute of Health (NIH) in cases when the information gathered for the research could be held against the research participant in a court of law. An investigator applies for a certificate of confidentiality through the NIH. The NIH will review the application and make a determination as to whether or not a CoC may be granted for the specific research project.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA for audit purposes. Consequently, the IRB may require that these conditions for release be stated clearly and explicitly in the informed consent document.

Additional information, regarding CoCs, including the application information necessary for applying for a Certificate of Confidentiality may be obtained on the NIH website.

3.8.11 Compliance with all Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and the IRB rely on the University Counsel for the interpretation and application of State law and the laws of any other jurisdiction where research is conducted as they apply to human participants research.

All consent forms must be consistent with applicable state and local laws.

3.9 Possible IRB Actions

Approval - the study is approved as submitted.

Specific minor revisions - the protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided or potentially ambiguous language that needs clarification. For full review, the needed revisions are agreed upon at the meeting when the protocol is reviewed. For expedited review, they are designated by the reviewer(s). These revisions are presented to the PI for incorporation by simple concurrence.

In order to receive approval for a protocol deferred for non-substantive issues:

1. For full review, the investigator's response, the revised protocol and the previously submitted protocol is reviewed by the IRB Chair, Vice Chair, or designee. The reviewer(s) may accept the revisions upon receipt and determination of adequacy without further action by the IRB.
2. For expedited, the investigator's response, the revised protocol and the previously submitted protocol is given to the same reviewer(s) for re-review.
3. Approval of the protocol application will not be granted until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).
4. The outcome of the IRB's deliberations is communicated to the investigator in writing.

Note: For full review, the expiration date for the protocol is calculated based on the date that the convened IRB reviewed the protocol and NOT on the final approval date.

Deferred for substantive issues - regarding the protocol and/or consent form must be addressed. This action is taken if substantial modification or clarification is required, or

insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research must not occur until subsequent review by the convened IRB or the expedited reviewer(s) of the material the PI submitted.

In order to receive approval for a protocol deferred for substantive issues:

1. For full review, the investigator's response must be submitted for review at a subsequent, convened meeting of the same IRB. RPO provides the IRB with the investigator's response and the revised protocol. The item is placed on the agenda for re-review at the next meeting.
2. For expedited review, the investigator's response, the revised protocol, and the previously submitted protocol are given to the same reviewer(s) for re-review.
3. Approval of the protocol application will not be granted until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).
4. The outcome of the IRB's deliberations is once again communicated to the investigator in writing.
5. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the IRB meeting or in the file for expedited review.

Disapproved - The IRB has determined that the research cannot be conducted by employees or agents of the University or otherwise under the auspices of the University.

3.10 Study Suspension and Termination

3.10.1 Suspension/Termination

The IRB may vote to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unanticipated problems or serious harm to participants or others. (See Section 8 for a discussion of unexpected problems.)

Suspension of IRB approval is a directive of the convened IRB or IRB Chair or RPO Director either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

The IRB Chair or RPO Director may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or RPO Director must be reported to a meeting of the convened IRB.

Research may be terminated only by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will consider notification of any participants currently participating that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled participants are necessary to protect the rights and welfare of participants, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of participants for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that the participants should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

3.11 Continuing Review

The IRB will conduct a continuing review of ongoing research at intervals that are appropriate to the level of risk for each research protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur even when the remaining research activities are limited to the analysis of private identifiable information.

3.11.1 Approval Period

At Brown University, determination of the approval period and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several participants.

For each initial or continuing approval the IRB will indicate an approval period with an approval expiration date specified. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB approved the research or the date the convened IRB deferred the research for non-substantive issues. For a study approved

under expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

The approval date and approval expiration date are clearly noted on all IRB certifications sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review of the entire protocol must occur.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

3.11.2 Continuing Review Process

To assist investigators RPO staff will send out renewal notices to investigators two months in advance of the expiration date; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

- protocol renewal form;
- current consent document(s); and
- other documents, as necessary.

In conducting continuing review of research not eligible for expedited review, IRB members are provided, and review, all of the above material. The reviewer for that month will review the complete protocol, including any amendments previously approved by the IRB. At the meeting, the monthly reviewer leads the IRB through the completion of the regulatory criteria for approval.

RPO staff attends the convened meetings and brings the complete protocol files for each protocol on the agenda. The IRB staff will retrieve any additional related materials the IRB members request.

In the case of expedited review, the IRB members may request the IRB office staff to provide them with any additional materials required for the review.

Review of currently approved consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

3.11.3 Expedited Review of Continuing Review

In conducting continuing review under expedited review, the reviewers receive all of the above material. The reviewer(s) determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 (see Expedited Review Categories). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

3.11.4 Lapse in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual participants to continue participating in the research interventions or interactions. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.

RPO is responsible for immediately notifying the investigator of the expiration of approval and that all research activities must stop.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval the PI must immediately submit to the IRB Chair a list of research participants for whom suspension of the research would cause harm. Enrollment of new participants cannot occur and continuation of research interventions or interactions for already enrolled participants should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual participants to do so.

Failure to submit continuing review information on time is non-compliance and will be handled according to the non-compliance policy.

If the study is FDA-regulated, the IRB Chair must follow FDA requirements in 21 CFR 56.108(b)(3) in making their decision.

The sponsoring agency, private sponsor, or other Federal agencies must be informed, as appropriate.

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 30 days and the PI has not

provided the required continuing review information, the PI must submit a new application to the IRB for review and approval. If the study approval has lapsed 30 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If a research protocol receives contingent approval at the time of the continuing review and the approval expires before the PI responds to the contingencies, the PI may not enroll any new participants after the approval expiration date. Once the PI responds, the existing protocol will be reviewed for continuation. If the PI does not respond for an extended period, the IRB may vote to administratively close the study. Decisions of this kind must be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing treatment as part of the research study.

3.12 Amendment to an Approved Protocol

Investigators may wish to modify or amend their approved protocols. Investigators must seek IRB approval before making any changes in approved research - unless the change is necessary to eliminate an immediate hazard to the participant (in which case the IRB must then be notified at once.)

In order to obtain approval, investigators must submit to the IRB documentation about the proposed changes to the status of the study, including, but not necessarily limited to:

- description of the changes
- reasons for the changes
- brief summary of the overall project
- revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to participants when such information might relate to their willingness to continue to participate in the study
- revised or additional recruitment materials
- any other relevant documents provided by the investigator
- revised Investigator's protocol application or sponsor's protocol (if applicable)

If the changes were requested by another IRB, study-related reasons for the changes must be provided, not simply a statement that another IRB requested them.

RPO staff will determine whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the amendment warrants full board review. The reviewer(s) using the expedited procedure has the ultimate responsibility to determine that the proposed changes may be approved through the expedited review procedure and, if not, must refer the amendment for full board review.

The requested changes must not be implemented until IRB approval has been granted, which is usually documented through a memo from RPO.

3.12.1 Expedited review of Protocol Amendments

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB Chair and/or designee(s) among the IRB members.

The reviewer(s) determine whether the amendments meet the criteria allowing review using the expedited procedure, and if so, whether the research with the proposed amendment meets the regulatory criteria for approval.

3.12.2 Full Board Review of Protocol Amendments

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research participants. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the participants' continued welfare.

All IRB members are provided with, and review, all documents provided by the investigator.

At the meeting, the primary reviewer presents an overview of the amendments and leads the IRB through the completion of the regulatory criteria for approval.

When the IRB reviews amendments to previously approved research, the IRB considers whether information about those amendments might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

3.13 Reporting IRB Actions

All IRB actions are communicated to the PI, or designated primary contact person for the protocol, in writing by the RPO staff. For an approval, written notification of approval will be sent. For a deferral, the notification will include the modifications required for approval along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision.

All letters to investigators will be filed in the protocol files maintained by RPO.

The IRB reports its findings and actions to the Institution in the form of its minutes which are stored permanently and securely in the RPO Office. Copies of minutes are distributed by RPO staff to the Brown University Institutional Official (IO).

3.14 Appeal of IRB Decisions

When an IRB protocol presented at a convened meeting is disapproved, deferred or requires minor modifications, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

In cases where there is disagreement between the IRB and the PI regarding the nature and extent of the requested changes and these disagreements cannot be resolved amicably in an informal manner, the PI and/or the IRB may make an appeal to the IO for a resolution of the matter. The IO may organize a meeting to help facilitate discussion between the IRB and the PI. While the IO may provide input and make recommendations to the IRB for expeditious resolution of the matter, final recommendations for approval remain under the purview of the IRB.

4 Documentation and Records

4.1 IRB Records

The IRB must prepare and maintain adequate documentation of the IRB's activities including, copies of all items reviewed, including, but not limited to:

- research protocols
- investigators' brochures, if any
- recruitment materials
- scientific evaluations (if any) that accompany the proposals
- approved consent documents, including DHHS-approved sample consent document and protocol, when they exist
- HIPAA Authorization documents if separate from the informed sample consent documents
- records of continuing review activities, including progress reports submitted by investigators
- any proposed amendments and the IRB action on each amendment
- reports of injuries to participants and serious and unexpected adverse events
- documentation of protocol violations
- documentation of non-compliance with applicable regulations
- statements of significant new findings provided to participants
- IRB membership roster(s)
- IRB meeting minutes
- Copies of all correspondence between the IRB and the investigator

IRB records must also document any determinations required by the regulations and protocol-specific findings supporting those determinations, including:

- waiver or alteration of the consent process
- research involving pregnant women, fetuses, and neonates
- research involving prisoners
- research involving children

4.2 IRB Membership Roster

A membership list of IRB members must be maintained. It must identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list must contain the following information about members:

1. Name
2. Earned degrees
3. Affiliated or non-affiliated status (neither the member nor an immediate family member of the member may be affiliated with the university)
4. Status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist). For purposes of this roster, IRB members with research experience are designated as scientists (including the student member). Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research. Students being trained in research fields will be designated as scientists.
5. Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; which IRB member is a prisoner representative (as required by Subpart C), and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations locally involved in research.
7. Role on the IRB (Chair, Vice Chair, etc.)
8. Voting status (Any *ex officio* members are non-voting members)
9. Alternate status, including the member they alternate with
10. Relationship (e.g., employment) between the individual IRB member and the organization

RPO must keep the IRB membership list current. The RPO Director, or designee, must promptly report changes in IRB membership to the Office for Human Research Protections, Departments of Health and Human Services.

4.3 IRB Minutes

Proceedings should be written and available for review by the next regularly scheduled IRB meeting date. Once approved by the members at a subsequent IRB meeting, the minutes must not be altered by anyone including a higher authority.

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
 - a. names of members present
 - b. names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions
 - c. names of absent members

- d. names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster)
- e. names of consultants present
- f. name of investigators present
- g. names of guests present

Note: The initial attendance list shall include those members present at any point during the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the number of members present for the vote on that item.

2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. Business Items discussed
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
6. Votes on these actions (total number voting; number voting for; number voting against; number abstaining; number of those excused; number of those recused)
7. Basis or justification for these actions including required changes in research
8. Summary of controverted issues and their resolution
9. Approval period for initial and continuing approved protocols, assumed to be 12 months unless otherwise indicated
10. Risk level of initial and continuing approved protocols
11. Review of interim reports, e.g. adverse event or safety reports, amendments, report of violation, etc.
12. Review of Data and Safety Monitoring Board (DSMB) summary
13. Applications that have met or not met requested stipulations
14. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.116(d)] when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent
15. Protocol-specific documentation that the research meets the required criteria [45 CFR 46.117(c)] when the requirements for documentation of consent are waived
16. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.

17. Determination of the risk level of investigational devices and the rationale for such determinations
18. Determinations of conflict of interest.
19. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research (e.g., Cooperative Studies, or other collaborative research).
20. Special protections warranted in specific research projects for groups of participants who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
21. A list of research approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol.
22. Documentation of approval by the Chair or designee of research contingent on specific minor conditions in the minutes of the first IRB meeting that takes place after the date of the approval.
23. An indication that, when an IRB member has a conflicting interest with the research under review, the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained.
24. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

A copy of the IRB-approved minutes for each IRB meeting will be distributed to the Institutional Official.

4.4 Documentation of Exemptions

Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request for satisfies the conditions of the cited exemption category.

4.5 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category, a description of action taken, if any, by the reviewer, and any determinations required by the regulations and protocol-specific findings supporting those determinations.

4.6 Record Retention

The above detailed records must be stored securely in RPO and must be retained for at least 3 years.

Records pertaining to research, which is conducted, must be stored securely in RPO and must be retained for at least three years after completion of the research. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least 3 years after closure.

After that time those records may be shredded or otherwise destroyed. All records must be accessible for inspection and copying by authorized representatives of the OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

Records are maintained in locked file cabinets and/or locked offices within RPO and are available only to IRB members, RPO staff, and senior officers as necessary.

5 Obtaining Informed Consent from Research Participants

5.1 Purpose

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of Brown University.

5.2 Definitions

Legally Authorized Representative. A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective participant for the participant's participation in the procedure(s) involved in the research. For the purposes of this policy, a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

Legal guardian. A person appointed by a court of appropriate jurisdiction.

5.3 Basic Requirements

No investigator may involve a human being as a participant in research without obtaining the legally effective informed consent of the participant or the participant's legally authorized representative unless a waiver of consent has been approved by the IRB. Except as provided in Section 5.9 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB (See Section 5.6).

Investigators must obtain consent prior to entering a participant into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent from a patient, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.

5.4 Informed Consent Process

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from participants who have the legal and mental capacity to give consent. For participants without that capacity, consent must be obtained from a legal guardian or a legally authorized representative.
2. The informed consent process shall be sought under circumstances that provide the participant (or legally authorized representative) with sufficient opportunity to consider whether or not to participate.
3. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
4. The informed consent information must be presented in language that is understandable to the participant (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research.
5. For participants whose native language is not English, informed consent must be obtained in a language that is understandable to the participant (or the participant's legally authorized representative). The IRB requires that informed consent conferences include a reliable translator when the prospective participant does not understand the language of the person who is obtaining consent.
6. The informed consent process may not include any exculpatory language through which the participant is made to waive, or appear to waive, any of the participant's legal rights or through which the investigator, the sponsor, the University, or University employees or agents are released from liability for negligence, or appear to be so released.
7. The PI is responsible for insuring that each prospective participant is adequately informed about all aspects of the research and understands the information provided.

5.5 Basic Elements of Informed Consent

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental; a description of any reasonably foreseeable risks or discomforts to the participant;
2. A description of any benefits to the participant or to others which may reasonably be expected from the research;
3. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;
4. A statement describing the extent, if any, to which confidentiality of records identifying the participant must be maintained;
5. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of research-related injury, including

who will pay for the treatment and whether other financial compensation is available;

6. An explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the participant;
7. Contact information for the IRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the participant wishes to talk to someone other than the research staff.
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled;
9. For FDA-regulated studies, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding participant confidentiality.

Additional elements of informed consent to be applied, as appropriate:

1. A statement that the particular procedure or treatment may involve risks to the participant, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to participants is not well known.)
2. A statement that if the participant is or becomes pregnant, the particular procedure or treatment may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a participant.)
4. Any additional costs to the participant that may result from participation in the research. (For example: Include when it is anticipated that participants may have additional costs.)
5. The consequences of a participant's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.)
6. Procedures for orderly termination of participation by the participant. (For example: Include when the protocol describes such procedures.)
7. A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)

8. The approximate number of participants involved in the study. (For example: Include when the research involves more than minimal risk.)

5.6 Documentation of Informed Consent

Except as provided in Section 5.9 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the participant or the participant's legally authorized representative at the time of consent.
2. A copy of the signed and dated consent form shall be given to the person signing the form.
3. The consent form may be either of the following:
 - a. A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the participant or the participant's legally authorized representative, but the participant or representative must be given adequate opportunity to read it before it is signed; or
 - b. A short form written consent document stating that the elements of informed consent have been presented orally to the participant or the participant's legally authorized representative.

When this method is used:

 - i. there must be a witness to the oral presentation; and
 - ii. the IRB must approve a written summary of what is to be signed by the participant or representative; and
 - iii. the witness must sign both the short form and a copy of the summary; and
 - iv. the person actually obtaining consent must sign a copy of the summary; and
 - v. a copy of the summary must be given to the participant or representative, in addition to a copy of the short form.

5.7 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being followed, or ensure that participants are truly giving informed consent.

Such monitoring may be particularly warranted for:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving highly vulnerable populations (e.g., children)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or

- Other situations when the IRB has concerns that consent process is not being conducted appropriately.

Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Chair and the RPO Director will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by IRB staff, IRB members or another party, either affiliated or not with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of participants. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately completed and documented,
- Whether the participant had sufficient time to consider study participation,
- Whether the consent process involved coercion or undue influence,
- Whether the information was accurate and conveyed in understandable language, and
- Whether the participant appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

5.8 Waiver of Informed Consent

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

- (a) The research involves no more than minimal tangible or intangible risk to the participants;
- (b) The waiver or alteration will not adversely affect the rights and welfare of the participants;
- (c) The research could not practicably be carried out without the waiver or alteration; and
- (d) Whenever appropriate, the participants must be provided with additional pertinent information after participation.

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waives the requirements to obtain informed consent, provided the IRB finds and documents that:

(a) 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:

1. public benefit or service programs
2. procedures for obtaining benefits or services under those programs
3. possible changes in or alternatives to those programs or procedures; or
4. possible changes in methods or levels of payment for benefits or services under those programs.

(b) The research could not practicably be carried out without the waiver or alteration.

FDA regulations do not provide for waivers of informed consent except in emergency situations (See Section 10.6.2).

5.9 Waiver of Documentation of Informed Consent

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

1. Only record linking the participant and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, and the research is not FDA-regulated, or only record linking the participant and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, or *Note 1:* Participants must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the participant is talking to researchers.)
Note 2: In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.
2. The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the participant, and the IRB will consider whether to require the investigator to provide participants with a written statement regarding the research.

6 Vulnerable Participants in Research

6.1 Purpose

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of Brown University.

6.2 Definitions

Children are persons who have not attained the legal age for consent to research, under the applicable law of the jurisdiction in which the research will be conducted.

Delivery means complete separation of the fetus from the woman by expulsion, extraction, or any other means.

Fetus is the product of conception from the time of implantation until delivery.

Viable fetus is now termed a “viable neonate.”

Non-viable fetus is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining heart and respiration. *NOTE: In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.*

Dead fetus is a fetus which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

In vitro fertilization is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

Neonate means newborn.

Viable neonate means being able, after delivery, to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).

Non-viable neonate means the same as a non-viable fetus.

Pregnancy is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

Prisoner is 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 that provide alternatives to criminal prosecution or

incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Surrogate Consent is consent obtained from a legally authorized representative on behalf of a participant determined to lack decision-making capacity.

6.3 Involvement of Vulnerable Populations

When some or all of the participants in a protocol are likely to be vulnerable to coercion or undue influence, the IRB should include additional safeguards to protect the rights and welfare of these participants. Some of the vulnerable populations that might be involved in research include children, pregnant women, fetuses, neonates, prisoners, or adults who lack the ability to consent, students, employees, or homeless persons.

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, best efforts will be made to ensure that the review process will include one or more individuals who are knowledgeable about or experienced in working with these participants. For example, the IRB will include one or more individuals who are knowledgeable about or experienced in working with children, prisoners, or adults with limited decision-making capacity, when reviewing research that involves individuals from these populations.

45 CFR 46 has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs.

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Participants
- Subpart D - Additional Protections for Children Involved as Subjects in Research

DHHS-funded research that involves any of these populations must comply with the requirements of the relevant subparts. Research funded by other federal agencies may or may not be covered by the subparts.

6.4 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable participants in the research proposal. The PI is responsible for identifying participants who are at risk for impaired decisional capacity and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or ad hoc consultants, individual(s) interested in or who have experience with the vulnerable populations involved in a research proposal.
3. The IRB reviews the PI's justifications for including vulnerable populations in the research to assess appropriateness of the research proposal.

4. The IRB must ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable participants as needed at the time of initial review of the research proposal.
5. The IRB shall continue to review research at intervals appropriate to the degree of risk and determine whether the proposed research continues to fulfill criteria for approval. Information reviewed should include the number of participants considered as members of specific vulnerable populations.
6. For studies that do not have or are not required to have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee and have entered vulnerable participants, the IRB needs to carefully review a data and safety monitoring plan.
7. The IRB should be knowledgeable about and experienced in working with populations who are vulnerable to coercion and undue influence. If the IRB requires additional qualification or expertise to review a protocol, it should obtain consultation.

6.5 Procedures

1. Initial Review of Research Proposal:

1. The PI should identify the potential to enroll vulnerable participants in the proposed research at initial review and provide the justification for their inclusion in the study.
2. The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a data and safety monitoring board or data monitoring committee as appropriate.
5. The PI should provide appropriate safeguards to protect the participant's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the participant's capacity to provide voluntary informed consent.
 - a. Examples of studies that may warrant independent monitoring include those involving schizophrenic patients who will be exposed to placebo, drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations that may also warrant independent monitoring would include individuals with dementia, schizophrenia, other psychotic disorders or conditions characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders.
6. The IRB assesses the adequacy of additional protections for vulnerable populations provided by the PI.

2. Continuing Review and Monitoring. At continuing review the PI should identify, in the progress report, the number of vulnerable participants enrolled and any that need an independent monitor.

6.6 Research Involving Pregnant Women, Human Fetuses and Neonates

6.6.1 Research Involving Pregnant Women or Fetuses

6.6.1.1 Research Not Funded by DHHS

For research not funded by DHHS, no additional safeguards are required and there are no restrictions on the involvement of pregnant women in research where the risk to the fetus is no more than minimal.

Pregnant women or fetuses may be involved in research not funded by DHHS involving more than minimal risk to fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. 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;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.6.1.2 Research Funded by DHHS

For DHHS-funded research, 45CFR46 Subpart B applies to all research involving pregnant women. Under 45CFR46 Subpart B, pregnant women or fetuses may be involved in research funded by DHHS if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4. or 5. of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 10.1.3;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.6.2 Research involving neonates

Neonates of uncertain viability and non-viable neonates may be involved in research if all of the following conditions are met:

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

2. each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. individuals engaged in the research will have no part in determining the viability of a neonate.
4. the requirements of Neonates of Uncertain Viability or Non-viable Neonates (see below in this section) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

The IRB determines that:

1. the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
2. the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
3. the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions of permission and assent, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

Non-viable Neonates. After delivery, non-viable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1. vital functions of the neonate will not be artificially maintained;
2. the research will not terminate the heartbeat or respiration of the neonate;
3. there will be no added risk to the neonate resulting from the research;
4. the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. the legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.
6. however, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a non-viable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a non-viable neonate will not suffice to meet the requirements of this paragraph.

Viable Neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of IRB review process and research involving children.

6.6.3 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

1. Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
2. If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research participants and all pertinent sections of this manual are applicable.

6.6.4 Research Not Otherwise Approvable

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates and the research is not approvable under the above provisions, then the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

- a. that the research in fact satisfies the conditions of Section 6.6.1, as applicable; or
- b. the following:
 - 1) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
 - 2) the research will be conducted in accord with sound ethical principles; and
 - 3) informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

6.7 Research Involving Prisoners

Prisoners are another of the three classes that are deemed so vulnerable to exploitation in research that there are special rules protecting them. In the past, prisoners were viewed as a convenient research population.

The concern Subpart C, and this document based on Subpart C, attempts to address is whether prisoners have any real choice in participation in research or whether incarceration prohibits free choice.

6.7.1 Applicability

This policy applies to all research conducted under the auspices of Brown University involving prisoners as participants. Even though a University IRB may approve a research protocol involving prisoners as participants according to this policy, investigators are still subject to the administrative regulations of the appropriate State Department of Corrections and any other applicable State or local law. [45 CFR 46.301]

6.7.2 Minimal Risk

The definition of minimal risk in Subpart C is different than in the rest of the federal regulations. According to 45CFR46.303, minimal risk is 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.

6.7.3 Composition of the IRB

[45 CFR 46.304]

In addition to satisfying the general requirements detailed in the IRB section of this manual, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB.
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

6.7.4 Additional Duties of the IRB

[45 CFR 46.305]

In addition to all other responsibilities, the IRB will review research involving prisoners and approve such research only if it finds that:

1. the research falls into one of the following permitted categories [45 CFR 46.306]:
 - a. 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 participants;
 - b. 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 participants;
 - c. research on conditions particularly affecting prisoners as a class (for example, research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults);
 - d. research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the participant.

2. 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;
3. the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
4. 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 to the IRB justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
5. the information is presented in language which is understandable to the participant population;
6. adequate assurance exists that parole board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7. where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

6.7.5 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies that meet the following criteria:

- (1) in which the sole purposes are
 - (i) to describe the prevalence or incidence of a disease by identifying all cases, or
 - (ii) to study potential risk factor associations for a disease, and
- 2) where the IRB has approved the research and fulfilled its duties under 45CFR 46.305(a)(2)–(7) and determined and documented that
 - (i) the research presents no more than minimal risk and no more than inconvenience to the prisoner-participants, and
 - (ii) prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45CFR46.306(a)(2).

The range of studies to which the waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the participants.

In order for a study to be approved under this waiver, the IRB would need to ensure that, among other things, there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of the data.

6.8 Research Involving Children

6.8.1 Allowable Categories

Research on children must be reviewed and categorized by the IRB into one of the following groups:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., minimal risk). [45 CFR 46.404]
 - The IRB may find that the permission of one parent is sufficient.
 - Assent, as necessary, of a child capable of providing assent based on age and/or cognitive capacity.
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participant. [45 CFR 46.405]
 - The risk is justified by the anticipated benefit to the participants;
 - The IRB may find that the permission of one parent is sufficient;
 - Assent, as necessary, of a child capable of providing assent based on age and /or cognitive capacity.
3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual participant, but likely to yield generalizable knowledge about the participant's disorder or condition. [45 CFR 46.406]
 - The risk represents a minor increase over minimal risk;
 - The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
 - Permission of either both parents, or legal guardian, is required- unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child;
 - Assent, as necessary, of a child capable of providing assent based on age and/or cognitive capacity.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. [45 CFR 46.407]

- Federally-funded research in this category must be approved by the Secretary of Health and Human Services, and requires consent of either both parents, or legal guardian.
- For non-federally-funded research, IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
 1. That the research in fact satisfies the conditions of the previous categories, as applicable; or
 2. The following:
 - i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
 - ii. The research will be conducted in accord with sound ethical principles; and
 - iii. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

6.8.2 Parental Permission and Assent

6.8.2.1 Parental Permission

In accordance with 45CFR46.408(b) the IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent as stated in 45CFR46.116(a)(1-8) and any additional elements the IRB deems necessary.

The IRB may find that the permission of one parent is sufficient for research to be conducted under 45CFR46.404 or 45CFR46.405. The IRB's determination that consent must be obtained from both parents will be documented when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under 45CFR 46.406 and 45CFR46.407 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.

The IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

- the research meets the provisions for waiver in 45CFR46.116(d)(1-4) and if the IRB determines that the research protocol is designed for conditions or a

participant population for which parental or guardian permission is not a reasonable requirements to protect the participants (for example, neglected or abused children).

- an appropriate mechanism for protecting the children who will participate as participants in the research is substituted, and that the waiver is not inconsistent with Federal State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by 45CFR46.117.

6.8.2.2 Assent from Children

Because “assent” means a child’s affirmative agreement to participate in research, (45 CFR46.402(b), the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved. The Brown University IRB has the discretion to judge children’s capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective participants. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script and/or reading the document with the child, would be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual

exceptions to these guidelines, when assent is less obligatory due to study procedures involving treatment for serious health conditions (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research participants, even when their parents consent to it.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement under certain circumstances.

The Assent Form

Researchers should try to draft a form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. tell why the research is being conducted;
2. describe what will happen and for how long or how often;
3. say it's up to the child to participate and that it's okay to say no;
4. explain if it will hurt and if so for how long and how often;
5. say what the child's other choices are;
6. describe any good things that might happen;
7. say whether there is any compensation for participating; and
8. ask for questions.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

6.8.2.3 Children Who Are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition, only if such research is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis*.

The advocate must 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.

6.9 Persons with Impaired Decision Making Capacity

Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. Only incompetent persons or persons with impaired decision making capacity are suitable as research participants. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as participants. Incompetent persons or persons with impaired decision-making capacity must not be participants in research simply because they are readily available.
2. The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be participants of research that imposes a risk of injury, unless that research is intended to benefit that participant and the probability of benefit is greater than the probability of harm.
3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent participants or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the participant would do if competent, or if the participant's wishes cannot be determined, what they think is in the incompetent person's best interests.

6.9.1 Determination of Decision-Making Capacity

The decision-making capacity of a potential research participant should be evaluated when there are reasons to believe that the participant may not be capable of making voluntary and informed decisions about research participation.

The investigator and research staff must have adequate procedures in place for assessing and ensuring participants' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate.

For research protocols that involve participants with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.

For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential participants have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential participants' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research participants with mental disorders.

For research protocols involving participants who have fluctuating or limited decision making capacity the IRB may ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the participant to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess participant understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, interpreter for hearing-impaired participants, allowing a waiting period before enrollment, or involvement of a trusted family member or friend in the disclosure and decision making process.

Both investigators and IRB members must be aware that for some participants, their decision-making capacity may fluctuate. For participants with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may participants be forced or coerced to participate.

In the event research participants become incompetent or impaired in decision making capacity after enrollment, the PI is responsible for notifying the IRB and RPO. The PI is

responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research participants.

6.9.1.1 Determining Capacity to Consent

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

- ability to evidence a choice,
- ability to understand relevant information,
- ability to appreciate the situation and its likely consequences, and
- ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias, or other impairing conditions, and qualified to assess and monitor capacity and consent in such participants on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The majority of studies conducted at Brown University only allow enrolling participants who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess capacity of each potential participant to consent. The PI may determine after appropriate medical evaluation that the prospective research participant lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

A person who has been determined to lack capacity to consent to participate in a research study must be notified of that determination before permission may be sought from his or her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential participant must then be notified. Should the person object to participating, this objection should be heeded.

6.9.2 Informed Consent and Assent

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and document in accordance with Section 5 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a participant (surrogate consent) as described below.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the research to the extent compatible with the participant's understanding and, if possible, the participant should

give their assent to participate, sign and date the written informed consent or a separate assent form. If the person objects to participating, this objection should be heeded.

Both investigators and IRB members must be aware that for some participants, their decision-making capacity may fluctuate. For participants with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may participants be forced or coerced to participate.

6.9.3 Surrogate Consent

The regulations generally require that the investigator obtain informed consent from participants. Under appropriate conditions, investigators also may obtain informed consent from a *legally authorized representative* of a participant (surrogate consent).

Definition: *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research [45 CFR 46.102(c)].

This policy is designed to protect human participants from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity.

Surrogate consent may be obtained from a court appointed guardian of the person or a health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC). For example, a participant might have designated an individual to provide consent with regard to health care decisions through a durable power of attorney and have specified that the individual also has the power to make decisions on entry into research.

7 Investigational Drugs & Devices in Research

7.1 Purpose

The following procedures describe the use of investigational drugs and devices in research under the auspices of Brown University. Use of investigational drugs must be conducted according to FDA IND regulations, 21CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21CFR Part 812, and other applicable FDA regulations.

7.2 Definitions

Investigational Drug. An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21CFR Part 312) or an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

Investigational Device. is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

IND. IND means an investigational new drug application in accordance with 21CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21CFR 812.

Emergency Use. Emergency use is defined as the use of an investigational drug or biological product with a human participant 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.

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

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a participant; or
- (2) 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 participant; or
- (3) 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 participant; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

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

Humanitarian Use Device (HUD). Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year.

7.3 FDA Exemptions

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

1. 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. [21CFR §56.104(c)]
2. 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. [21CFR §56.104(d)]

7.4 IND/IDE Requirements

When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, an Investigational New Drug (IND) or Investigational Device Exemption (IDE) may be required.

If the protocol involves investigational drugs or devices, the investigator will be asked if there is an IND/IDE for the research and document assurances from the Sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

1. Industry sponsored protocol with IND/IDE
2. Letter from FDA
3. Letter from industry sponsor

If the research involves drugs or devices and there is no IND/IDE, the investigator will be asked for a rationale as to why it is not required.

For drugs, an IND may not be necessary if all seven of the following conditions are met:

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;

4. The research does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7];
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

For devices, an IDE may not be necessary if:

1. There is a claim that it is a Non-significant risk device (NSR);
2. The research involves a device when used or investigated in accordance with the indications in labeling in effect at that time;
3. The research involves a device 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 21 CFR 807 in determining substantial equivalence;
4. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
 - a. Is noninvasive,
 - b. Does not require an invasive sampling procedure that presents significant risk,
 - c. Does not by design or intention introduce energy into a participant, and
 - d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
5. The research involves 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;
6. The research involves a device intended solely for veterinary use;
7. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
8. The research involves 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.

The IRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If there are drugs or devices involved, but no IND/IDE, whether the research meets the above criteria.

7.5 Responsibilities

7.5.1.1 Investigator

1. The investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines and must obtain approval from the Brown University IRB.
2. The investigator proposing the drug/device research will be required to provide a plan, that will be evaluated by the IRB, that will include: (a) storage, (b) security, (c) dispensing.
3. The investigator is responsible for the investigational drug/device accountability which includes storage, security, dispensing, administration, return, disposition and records of accountability. The investigator will delegate the responsibility for drugs/biologic accountability to the pharmacy service.
4. If because of special circumstances, an investigational drug/device is not stored in the pharmacy, the investigator is responsible for the storage, security and dispensing of the drug/device. The investigator must complete and submit an investigational control sheet containing information on the plan for storage, security and dispensing of the drug/device to the IRB prior to its approval of the study. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of investigator's control. Proper instructions on the use of the drug/device must be provided to the participants. A log must be kept regarding the receipt, use and/or dispensing of the drug/device and the disposition of remaining devices at the conclusion of the investigation.
5. The investigator shall report all unanticipated problems involving risk to participants or others to the IRB according to the procedures in this document.
6. For research involving investigational new drugs:
 - a) The PI is responsible for informing the pharmacy service that IRB approval has been obtained. In addition a signed copy, of the consent form must be sent to pharmacy service to document each participant's consent to participate in the study.
 - b) The PI must inform the pharmacy service when a study involving investigational drugs has been terminated.
 - c) The investigator shall report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug according to the procedures in the protocol.
7. For research involving investigational devices:

- a) If a device considered NSR by the investigator or sponsor, is determined to have significant risk upon IRB review, the investigator is responsible for notifying the sponsor of the IRB's determination upon receipt of written notice. The PI should provide the IRB with confirmation of this action.
 - b) A copy of the protocol approval by the FDA and the IRB and the consent must be provided to the pharmacist if the device will be stored in the pharmacy. A request for the IDE and a copy of the signed consent from the research participant must be provided to the pharmacist when the device is required for use. If the investigator is storing the devices, a log must be maintained to indicate name of participant, date dispensed, by whom it was dispensed, amount remaining, and who received the device.
 - c) The investigator shall submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
8. Following completion of the study, the termination procedure for investigational drugs must be applied if under pharmacy control. If the devices are kept by the investigator, the log must be completed regarding the receipt, use and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
 9. When an investigator files an IND or IDE, the investigator is considered the sponsor and as such carries all of the FDA regulatory responsibilities and reporting obligations of both the Investigator and sponsor as described in the FDA regulations. The investigator will affirm that they are aware of and will comply with the regulatory responsibilities of a sponsor.

7.5.1.2 IRB

1. The IRB must review the research in accordance with these requirements and needs to use the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).
2. For research involving investigational devices:
 - a) The IRB is responsible for reviewing the protocol and determining if the device represents significant risk (SR) or non-significant risk (NSR) and report the findings to the investigator in writing. The IRB must consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If a study that has been submitted as NSR is considered SR, the IRB must recommend that an IDE be obtained.
 - b) Protocols involving significant risk devices do not qualify for expedited review.

- c) The IRB must document in the Minutes the rationale for the determination of a device that is classified as NSR/SR.
- d) The IRB will provide written documentation of approval to the investigator with a determination of whether the device presents a significant or non-significant risk.

7.6 Emergency Use

7.6.1 Emergency Exemption from Prospective IRB Approval.

FDA defines emergency use as the use of an investigational drug or biological product with a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Informed consent is required unless the conditions for exemption are met. The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review.

If the PI notified the IRB prior to the emergency use of an investigational test article, the circumstances will be reviewed by IRB staff to determine that it meets FDA regulations and the investigator will be advised accordingly. All after-the-fact reports to the IRB of emergency use will be reviewed by IRB staff to determine the circumstances and for compliance with FDA regulations.

7.6.2 Emergency Waiver of Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- a. The participant is confronted by a life-threatening situation necessitating the use of the test article;
- b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the participant;
- c. Time is not sufficient to obtain consent from the participant's legally authorized representative;
- d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the participant's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5-6 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB.

7.6.3 Treatment IND

FDA regulations (21 CFR 312.34 and 312.35) address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements.

7.6.4 Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

7.7 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived is covered by 21 CFR §50.24. The research plan must be approved in advance by the FDA or DHHS and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are not allowed under the regulations covering the emergency use of a test article in a life-threatening situation (21 CFR §56.104(c)).

7.8 Humanitarian Use Devices (HUD)

In accordance with 21 CFR 814.124, treatment with a HUD is subject to full board initial and continuing review by the IRB. At the time of review, the IRB will determine if written consent from participants for use of the HUD is necessary. If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, approval must be obtained from the appropriate local authority (such as the Chief of Staff), and the investigator is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use. It is the responsibility of the investigator to notify the FDA if the IRB were ever to withdraw approval for use of a HUD. The FDA should be notified within five days of notification of the withdrawal of approval. Investigators are reminded that Humanitarian Device Exemptions are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application.

8 Unanticipated Problems Involving Risks to Participants or Others and Adverse Events

8.1 Purpose

These procedures describe how the University complies with DHHS and FDA regulations which state that unanticipated problems involving risks to participants or others must be reported to the IRB, institutional officials, and relevant federal agencies and departments.

8.2 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to participants or others include any adverse event that is (1) unexpected, (2) serious, and (3) related or possibly related to participation in the research. Unanticipated problems also includes unexpected adverse events, regardless of severity, that the IRB determines represent risk to participants or others. Unanticipated problems also includes events that are not categorized as adverse events, are not directly related to an individual participant's participation in a study, but represent risk to participants or others.

Adverse Event. An adverse event (AE) is defined as any untoward physical or psychological occurrence in an individual participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article.

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Serious Adverse Event. A serious adverse event (SAE) is defined as death, a life threatening experience, hospitalization (for a person not already hospitalized), prolongation of hospitalization (for a patient already hospitalized), persistent or significant disability or incapacity, congenital anomaly and/or birth defects, or an event that jeopardizes the participant and may require medical or surgical treatment to prevent one of the preceding outcomes.

Unexpected Adverse Event. An unexpected adverse event (UAE) is any adverse event and/or reaction, the specificity or severity of which is not consistent with the risk information provided in the protocol, informed consent, current investigator brochure, or product labeling.

Adverse Device Effect. An adverse device effect (ADE) is any adverse event/effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol or the Investigator's Brochure.

Related. An event is "related" if it is likely to have been caused by the research procedures.

Substantive Action. An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status,

including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

Unexpected Death. The death of a research participant in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the participant's death. A participant's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of these procedures.

8.3 Data Safety Monitoring Plan

For all research that is more than minimal risk, the initial research plan submitted to the IRB should describe the procedures for safety monitoring, reporting of adverse events and/or unanticipated problems involving risks to participants or others, descriptions of interim safety reviews and the procedures planned for transmitting the results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB), if one exists, or an explanation why an independent data safety monitor is not necessary.

8.4 Procedures

8.4.1 Reporting

Investigators must report all possible unanticipated problems to the IRB within five (5) days of receiving notice of the event, if the event requires immediate intervention to prevent serious harm to participants or others. Investigators must report all other possible unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible and no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

Investigators must promptly report (according to the above schedule) the following events to the IRB if the events occur within thirty (30) days of participants' active participation:

- a. Adverse events which in the opinion of the principal investigator are both unexpected and related.
- b. An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk
- c. Information that indicates a change to the risks or potential benefits of the research. For example:
 - a. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
 - b. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.

- d. A breach of confidentiality.
- e. Incarceration of a participant in a protocol not approved to enroll prisoners.
- f. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- g. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- h. Protocol violation (meaning an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- i. Event that requires prompt reporting to the sponsor.
- j. Sponsor imposed suspension for risk.
- k. Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

8.4.2 Submission of Reports

Investigators or the study team must report possible unanticipated problems to RPO in writing. The written report should contain the following:

- a. Detailed information about the possible unanticipated problems, including relevant dates.
- b. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems is corrected and will not occur again.
- c. An assessment of whether any participants or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.
- d. Any other relevant information.
- e. Any other information requested by RPO.

A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded by RPO staff to the IRB Chair if the RPO staff believes that immediate intervention may be required to protect participants or others from serious harm.

Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the IRB director or RPO staff will notify the PI on the study when appropriate.

8.4.3 IRB Procedures for Handling Reports of Possible Unanticipated Problems

8.4.3.1 Review by IRB Staff and Chair

1) The IRB chairperson, and/or other experienced individuals designated by the IRB chairperson, receives and reviews the report of the event considered to be an unanticipated problem. The IRB chairperson (or designee) will make the final determination as to whether the event is to be regarded as an unanticipated problem. All events determined to be unanticipated problems will be reported to the relevant

regulatory agencies and institutional officials, as necessary, according to the procedures in this document.

2) Unanticipated problems for which no modifications to the protocol or informed consent process/documents are needed, as determined by the IRB chairperson (or designee), may be:

- (a) filed in the IRB records without further review by the convened IRB or,
- (b) at the discretion of the IRB chairperson (or designee) referred to the rest of the IRB members for review and further action, as appropriate, at a convened meeting.

For external adverse events, if the central monitoring entity or the PI did not propose any modifications to the protocol or informed consent process/document, but the IRB chairperson (or designee) believes that modifications are needed in response to the external adverse event(s), the IRB chairperson (or designee) requests in writing that the PI discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the IRB. These modifications then are handled in accordance with procedures below.

The IRB or the IRB chairperson (or designee) has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

3) Unanticipated problems for which modifications to the protocol or informed consent process/documents are needed, either as requested by the PI or determined by the IRB chairperson (or designee), will be handled as follows:

- (a) If all proposed modifications represent minor changes, the IRB chairperson (or designee) may review and, if appropriate, approve the modifications under an expedited review procedure. The related report of the external adverse event may be: (i) filed in the IRB records without further review by the convened IRB or, (ii) at the discretion of the IRB chairperson (or designee), referred to the rest of the IRB members for review and further action, as appropriate, at a convened meeting.
- (b) If any of the proposed modifications represent more than a minor change, or if the IRB chairperson (or designee) determines for any reason that he or she should not approve the proposed modifications under an expedited review procedure, the proposed modifications must be forwarded to the other IRB members for review at a convened meeting.

4) If the IRB chairperson (or designee) determines that modifications in addition to those proposed by the PI are needed in response to an external adverse event, the IRB chairperson (or designee) requests in writing that the PI submit a response or the necessary additional modifications for review by the IRB.

8.4.3.2 IRB Review

1. All IRB members will receive the event report. The full IRB will make findings and recommendations based on the following considerations:
 - a. whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
 - b. what action in response to the report is appropriate.
 - c. whether suspension or termination of approval is warranted.
 - d. whether further reporting to Institutional and/or federal officials is required.
2. If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. no action
 - b. requiring modifications to the protocol
 - c. revising the continuing review timetable
 - d. modifying the consent process
 - e. modifying the consent document
 - f. providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
 - g. providing additional information to past participants
 - h. requiring additional training of the investigator and/or study staff
 - i. other actions appropriate for the local context
3. If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:
 - a. requiring modifications to the protocol
 - b. revising the continuing review timetable
 - c. modifying the consent process
 - d. modifying the consent document
 - e. providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
 - f. providing additional information to past participants
 - g. requiring additional training of the investigator and/or study staff

- h. reconsidering approval
 - i. requirement that current participants re-consent to participation
 - j. monitoring of the research
 - k. monitoring of the consent
 - l. referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
 - m. suspending the research
 - n. terminating the research
 - o. other actions appropriate for the local context
4. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the IO, and OHRP, and FDA (if FDA-regulated research) through the IO. This should be done in writing.
 5. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will:
 - a. notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, and the investigator's supervisor, and
 - b. report its findings and recommendations to the Vice President for Research for further reporting to the appropriate federal officials (ORO, OHRP, and FDA).

8.4.3.3 Reconsideration of the IRB Decision

The notice to the investigator of the IRB determination will inform the investigator that he or she has ten (10) business days from receipt of the notice to request reconsideration of the IRB decision by sending the IRB a written request for reconsideration including the basis of the investigator's request.

- a. If an investigator requests reconsideration, the investigator's written request is considered at the next available IRB meeting; and the IRB makes a determination whether to uphold, reverse or modify its decision. The IRB notifies the investigator of the final outcome.
- b. If the IRB receives a request for reconsideration from the investigator, the IRB should notify the Vice President for Research of the request and of the final outcome.

9 Complaints and Non-compliance

9.1 Purpose

The following procedures describe how complaints, allegations of non-compliance, suspensions and terminations of IRB approval are handled by the IRB.

9.2 Definitions

Non-compliance. Non-compliance is defined as failure to comply with any of the regulations and policies described in this document and failure to follow the determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.

Serious non-compliance. Serious non-compliance is defined as failure to follow any of the regulations and policies described in this document or failure to follow the determinations of the IRB and which, in the judgment of either the IRB Chair or the convened IRB, increases risks to participants, decreases potential benefits, or compromises the integrity of the human research protection program. Research being conducted without prior IRB approval is considered serious noncompliance.

Continuing non-compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the IRB Chair or convened IRB, suggests a likelihood that instances of non-compliance will continue without intervention. Continuing non-compliance also includes failure to respond to a request to resolve an episode of non-compliance.

Allegation of non-compliance. Allegation of non-compliance is defined as an unproved assertion of non-compliance.

Finding of non-compliance. Finding of non-compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator that the protocol was willfully not followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance.)

Suspension. A suspension is directive of the convened IRB or IRB designee either to stop temporarily some or all previously approved research activities or to stop permanently some previously approved research activities. Suspended protocols remain open and require continuing review. A lapse of approval due to a lack of continuing review is not considered a suspension for these procedures.

Termination. A termination is a directive of the convened IRB or IRB designee to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

9.3 Complaints

The Chair of the IRB or the RPO Director will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB. This includes complaints, concerns, and appeals from investigators, research participants, and others.

If the complaint meets the definition of non-compliance, it will be considered an allegation.

9.4 Non-compliance

All investigators conducting research as employees or agents of Brown University are expected to comply with the highest standards of ethical and professional conduct in accordance with federal and state regulations and IRB policies governing the conduct of research involving human participants.

The Principal Investigator is responsible for reporting any non-compliance by study personnel to the IRB.

9.4.1 Review of Allegations of Non-compliance

All allegations of non-compliance will be reviewed by the IRB Chair and the RPO Director. They will review:

1. all documents relevant to the allegation;
2. the last approval letter from the IRB;
3. the last approved IRB application and protocol;
4. the last approved consent document;
5. the grant, if applicable; and
6. any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

The IRB Chair and RPO Director will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question.

If in the judgment of the IRB Chair and RPO Director, the reported allegation of non-compliance is not true, no further action will be taken. If in the judgment of the IRB Chair and RPO Director, the reported allegation of non-compliance is true, the non-compliance will be processed according to Section 7.4.2 Review of Findings of Non-compliance.

If in the judgment of the IRB Chair and RPO Director, any allegation or findings of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB Chair or RPO Director may suspend the research as described in Section 3.10 with subsequent review by the IRB.

9.4.2 Review of Findings of Non-compliance

If in the judgment of the IRB Chair and RPO Director, the reported finding of non-compliance is not serious, not continuing, and the proposed corrective action plan seems adequate, no further action is required; and the IRB is informed at the next convened meeting. Otherwise, the matter will be presented to the IRB at a convened meeting with a recommendation that a formal inquiry (described below) will be held.

All findings of non-compliance referred to the IRB will be reviewed at a convened meeting. All IRB members will receive:

1. all documents relevant to the allegation;
2. the last approval letter from the IRB;
3. the last approved IRB application; and
4. the last approved consent document.

At this stage, the IRB may:

1. find that there is no issue of non-compliance;
2. find that there is non-compliance that is neither serious nor continuing and an adequate corrective action plan is in place;
3. find that there may be serious or continuing non-compliance and direct that a formal inquiry (described below) be held; or
4. request additional information.

9.4.3 Inquiry Procedures

A determination may be made by the IRB that an inquiry is necessary based on several issues that may include but are not limited to:

1. participants' complaint(s) that rights were violated;
2. report(s) that the investigator is not following the protocol as approved by the IRB;
3. unusual and/or unexplained adverse events in a study; and/or
4. repeated failure of investigator to report required information to the IRB.

A subcommittee is appointed consisting of IRB members, and non-members if appropriate, to ensure fairness and expertise. The subcommittee is given a charge by the IRB, which can include any or all of the following:

1. review of protocol(s) in question;
2. review of sponsor audit report of the investigator, if appropriate;
3. review of any relevant documentation, including consent documents, case report forms, participants' investigational and/or medical files etc., as they relate to the investigator's execution of her/his study involving human participants;
4. interview of appropriate personnel if necessary;
5. preparation of either a written or oral report of the findings, which is presented to the full IRB at its next meeting;

6. recommend actions if appropriate.

9.4.4 Final Review

The results of the inquiry will be reviewed at a convened IRB meeting where the IRB will receive a report from the subcommittee. If the results of the inquiry substantiate the finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

1. request a correction action plan from the investigator;
2. verification that participant selection is appropriate and observation of the actual informed consent;
3. an increase in data and safety monitoring of the research activity;
4. request a directed audit of targeted areas of concern;
5. request a status report after each participant receives intervention;
6. modify the continuing review cycle;
7. request additional investigator and staff education;
8. notify current participants, if the information about the non-compliance might affect their willingness to continue participation;
9. require modification of the protocol;
10. require modification of the information disclosed during the consent process;
11. require current participants to re-consent to participation;
12. suspend the study (see below); or
13. terminate the study (see below).

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 10.

9.4.5 Additional Actions

A finding of serious or continuing non-compliance may also result in the following sanctions, among others:

1. suspension or termination of IRB approval of specific research protocols or of all research involving human participants in which the investigator participates;
2. sponsor actions - in making decisions about supporting or approving applications or proposals covered by this policy the Department of Health and Human Services or Agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension as described in Section 3.10, and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the Department of Health and Human Services or Agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human participants;

3. institutional or individual action by the federal OHRP. The OHRP may
 - a. withhold approval of all new studies by the IRB;
 - b. direct that no new participants be added to any ongoing studies;
 - c. terminate all ongoing studies, except when doing so would endanger the participants; and/or
 - d. notify relevant state, federal, and other interested parties of the violations.
4. individual disciplinary action of the investigator or other personnel involved in a study, up to and including dismissal, pursuant to University policies and procedures.

10 Reporting to Regulatory Agencies and Institutional Officials

10.1 Procedures

1. IRB staff will initiate these procedures as soon as the IRB takes any of the following actions:
 - a. determines that an event may be considered an unanticipated problem involving risks to participants or others
 - b. determines that non-compliance was serious or continuing
 - c. suspends or terminates approval of research
2. The Director or designee is responsible for preparing reports or letters which include the following information:
 - a. the nature of the event (unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of approval of research);
 - b. name of the institution conducting the research;
 - c. title of the research project and/or grant proposal in which the problem occurred;
 - d. name of the principal investigator on the protocol;
 - e. number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
 - f. a detailed description of the problem including the findings of the organization and the reasons for the IRB's decision;
 - g. actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend participant enrollment, terminate the research, revise the informed consent document, inform enrolled participants, increase monitoring of participants, etc.); and
 - h. plans, if any, to send a follow-up or final report by the earlier of
 1. a specific date; or
 2. when an investigation has been completed or a corrective action plan has been implemented
3. The IRB Chair and the IO review the letter and modify the letter/report as needed
4. The IO, or designee, is the signatory for all correspondence from the facility.
5. The Director or designee sends a copy of the report to:
 - a. The IRB by including the letter in the next agenda packet as an information item
 - b. The IO
 - c. The following federal agencies:

- OHRP, if the study is subject to DHHS regulations or subject to a DHHS federalwide assurance
 - FDA, if the study is subject to FDA regulations.
 - If the study is conducted or funded by any Federal Agency other than DHHS that is subject to “The Common Rule”, the report is sent to OHRP or the head of the agency as required by the agency
 - Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.
- d. Principal investigator
 - e. Sponsor, if the study is sponsored
 - f. Chairman or supervisor of the principal investigator
 - g. The Information Security Officer of an organization if the event involved violations of information security requirements of that organization
 - h. Office of Insurance and Risk, if appropriate
 - i. Others as deemed appropriate by the IO

The Director ensures that all steps of this policy are completed within 10 working days of the initiating action, whenever possible. For more serious actions, the Director will expedite reporting.

11 Investigator Responsibilities

11.1 Purpose

The following procedures describe the investigator responsibilities in the conduct of research involving human participants.

11.2 Investigators

Principal investigators are ultimately responsible for the conduct of research. Principal investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

Principal Investigators

At Brown University only faculty or staff members with University-paid appointments and graduate students (with an advisor's collaboration) may serve as the Principal Investigator on a research project involving human participants. Specific and unusual circumstances may arise where the Principal Investigator may have an unpaid University courtesy appointment.

The IRB recognizes one Principal Investigator (PI) for each study. The PI has ultimate responsibility for the research activities.

Protocols that require skills beyond those held by the Principal Investigator must be modified to meet the investigator's skills or have one or more additional qualified faculty as co-investigator(s).

Student Investigators

Undergraduate students may not serve as Principal Investigators. They must have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as PI and faculty advisor on the study.

[NOTE: It is unusual that an undergraduate project would meet the definition of "research" as defined earlier in this document for the purposes of human research projects, since for most undergraduate projects the primary intent of the data collection is to obtain a passing grade rather than to obtain data to "develop or contribute to generalizable knowledge".]

The RPO website contains the information needed to make the determination as to whether a project meets the human research definition of "research" and, therefore, requires IRB review. The faculty adviser, in conjunction with the student, will make the final determination regarding applicability.

Research Team

The research team consists of the PI and other individuals, also known as key personnel, who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol.

11.3 Responsibilities

In order to satisfy the requirements of this policy, investigators who conduct research involving human participants must:

- develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
- develop a research plan that is scientifically sound and minimizes risk to the participants;
- have sufficient resources necessary to protect human participants, including:
 - access to a population that would allow recruitment of the required number of participants
 - sufficient time to conduct and complete the research
 - adequate numbers of qualified staff
 - adequate facilities
 - a process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions
 - availability of medical or psychological resources that participants might require as a consequence of the research
- protect the rights and welfare of prospective participants;
- have plans to monitor the data collected for the safety of research participants;
- have a procedure to receive complaints or requests for additional information from participants and respond appropriately;
- ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and research staff;
- obtain and document informed consent as required by the IRB ensuring that no participant is involved in the research prior to obtaining their consent, as required by the approved protocol;
- ensure that all research involving human participants receives IRB review and approval in writing before commencement of the research;
- comply with all IRB decisions, conditions, and requirements;
- ensure that protocols receive timely continuing IRB review and approval;
- report unexpected or serious adverse event problems that require prompt reporting to the IRB (see Section 7);
- obtain IRB review and approval in writing before changes are made to approved protocols or consent forms; and

- seek IRB assistance when in doubt about whether proposed research requires IRB review;

11.4 Training / Ongoing Education of Investigators and Research Team

As stated above, one component of a comprehensive human research protection program is an education program for all individuals involved with research participants. Brown University is committed to providing training and an on-going educational process for investigators and members of their research team related to ethical concerns and regulatory and institutional requirements for the protection of human participants.

11.4.1 Orientation

All Principal Investigators and members of their research team (also known as “key personnel”) must review core training documentation including the “Brown University HRPP Policy and Procedures Manual,” and the “Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research.”

11.4.2 Initial Education

The PI and all applicable research personnel must complete the Brown University CITI Program in the Protection of Human Research Participants.

Research personnel include principal investigators, co-investigators, faculty advisors for student investigators, research assistants, and any research team members who have contact with research participants and/or their research data and identifiers.

New research protocols and applications for continuing review will not receive IRB approval until principal investigators have successfully completed the initial education requirement (or the continuing education requirement once the initial education requirement has been satisfied).

While research protocols and applications for continuing review will be accepted and reviewed if the Principal Investigator does not hold a current certification of training, final approval will not be granted until the PI has completed the initial education requirement (or the continuing education requirement once the initial education requirement has been satisfied).

11.4.3 Continuing Education and Recertification

All investigators and applicable research personnel must meet Brown University continuing education requirement every three(3) years after certification of initial education for as long as they are involved in human research. Acceptable training includes review of appropriate modules at the CITI web-based training site.

Investigators who are also IRB Chair, IRB members, or RPO staff will satisfy the training requirements for IRB members and staff described in this policy.

11.4.4 Additional Resources

Human research protection information will be made available on the RPO website on an ongoing basis to ensure that the University research community is apprised of current regulatory and policy requirements and training opportunities.

12 Special Topics

12.1 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, Rhode Island law mandates that certain persons who suspect child or elder abuse or neglect report this to the appropriate State agencies.

In situations where conditions of abuse or neglect might be revealed, mandated reporters should make themselves known as such to parents of children under age 18, to participants who are children, and to participants who are potential victims of abuse or neglect.

12.2 Brown University Students and Employees as Participants

When Brown University students and/or employees are being recruited as potential participants, researchers must ensure that there are additional safeguards for these participants. The voluntary nature of their participation must be primary and without undue influence on their decision. Researchers must emphasize to participants that neither academic status or grades, nor their employment, will be affected by their participation decision.

To minimize coercion, investigators should solicit participants through means such as bulletin board notices, flyers, advertisements, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g. administer a survey, investigators should do so at a time that would allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

12.3 Genetic Studies

Genetic research studies may create special risks to participants and their relatives. These involve medical, psychosocial, and economic risks, such as the possible loss of privacy, insurability, and employability, change in immigration status and limits on education options, and may create a social stigma. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members.

In studies involving genetic testing, several questions need to be addressed, including, but not limited to:

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed, such as mistaken paternity?
4. Does the participant or family member have the option not to know the results?
How will this decision be recorded?

5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the participant's right to withdraw from the research, withdraw data, and/or withdraw DNA?
7. Is the participant permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including, but not limited to:

1. Will DNA be stored or shared? If shared, will the participant's identity be known by the new recipient investigator?
2. Will the participant be contacted in the future by the investigator to obtain updated clinical information?
3. How can the participant opt out of any distribution or subsequent use of his/her genetic material?

12.4 Research Involving Coded Private Information or Biological Specimens

Brown University policy is based on the OHRP guidance document entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" (August 10, 2004 <http://www.hhs.gov/ohrp/humanparticipants/guidance/cdebiol.pdf>). This document:

- Provides guidance as to when research involving coded private information or specimens is or is not research involving human participants, as defined under HHS regulations for the protection of human research participants (45 CFR part 46).
- Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human research.
- Provides guidance on who should determine whether participants are involved in research.

For purposes of this policy, *coded* means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Under the definition of human participant in Section 2 of this policy, *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. This includes an investigator's use, study, or analysis for research purposes of identifiable private information or identifiable specimens already in the possession of the investigator.

In general, private information or specimens are considered to be individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. Private information or specimens are not considered to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Research involving **only** coded private information or specimens do **not** involve human participants if the following conditions are both met:

- (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals;

and

- (2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
 - (a) the key to decipher the code is destroyed before the research begins;
 - (b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); data use agreement
 - (c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
 - (d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(d) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforeseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human participants. Unless this research is determined to be exempt (See Section 7.2), IRB review of the research would be required. Informed consent of the participants also would be required unless the IRB approved a waiver of informed consent (See Section 9.3).

12.4.1 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Participants Research

The investigator in consultation with the IRB Chair or RPO staff, as necessary, will determine if the research involving coded information or specimens requires IRB review.