Institutional Review Board
Policies and Procedures

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1. **Introduction**

Hebrew SeniorLife (HSL, also referred to as ‘the Institution’) is a network of care for the elderly which includes Hebrew Rehabilitation Center (HRC), a 675-bed long-term care facility; three apartment complexes for seniors - Jack Satter House, Simon C. Fireman Community and Center Communities of Brookline; two continuing care retirement communities, Orchard Cove and NewBridge on the Charles; and the organization's Research and Training Institute, the Hinda and Arthur Marcus Institute for Aging Research (Marcus Institute). HSL also offers services to the community, including adult day health programs at HRC and in Brighton, MA, as well as short-term care services, and outpatient clinics in audiology, exercise, memory disorders, osteoporosis and rehabilitation. The Institution is dedicated to providing seniors with the highest quality of life through care, housing, research and training. All facilities are located in Massachusetts communities.

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

This Policy and Procedure manual applies to all research involving human participants conducted completely or partially at HSL facilities, conducted in approved off-site locations by HSL researchers, and/or conducted by HSL researchers while on official HSL time or business.

HSL researchers include but are not limited to employees, members of the research staff and members of the medical staff, including post-doctoral trainees. HSL researchers who are acting as ‘agents’ of HSL, who act on behalf of the Institution, or who reference their HSL appointment in relation to the protocol or publication are under the mandate of the HSL IRB.

HSL holds a FederalWide Assurance (FWA00000885) and an IRB Registration (IRB00001568) with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). HSL includes its housing sites (Hebrew Rehabilitation Center, Jack Satter House, Simon C. Fireman Community, Center Communities of Brookline, Orchard Cove, and NewBridge on the Charles) as components of its FWA.

### 1.1 IRB Authority

The HSL IRB has the following authority:

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

### 1.2 Ethical Principles

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

1.3 **Applicable Federal Regulations**

HSL complies with DHHS regulations at 45CFR46 and its subparts for the protection of human research participants. The regulations at 45CFR46 and its subparts provide the basis for review and approval of all research at HSL regardless of funding source, and where there is no external funding supporting the research.

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

The HSL IRB performs the functions that an IRB is required to perform in compliance with 45CFR160 and 164, and this policy for the use and disclosure of research participants protected health information.

1.4 **Applicable Commonwealth of Massachusetts Laws**

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

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

The IRB will consult with the General Counsel and Chief Compliance Officer in areas where federal and state regulations are not cohesive, when new or revised regulations or guidance are issued and require further interpretation, or when the application of federal or state laws is unclear given the facts of a specific circumstance.
1.5 IRB Autonomy

No individual or group of individuals may try to influence the deliberations and decisions of the IRB. IRB members may report any attempt to influence their decisions to the Institutional Official or the General Counsel and Chief Compliance Officer, and they will investigate any such reports.

1.6 Institutional Support and Responsibility for the IRB

To ensure an autonomous IRB and a compliant research program, Hebrew SeniorLife Administration is responsible for:

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

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

1.7 Institutional Official for the IRB

The Vice President for Research Administration serves as the HSL Institutional Official (IO). The IO reports to the Director of the Marcus Institute & Vice President for Academic Medicine, as well as the Chief Executive Officer of HSL. The budgets for the IRB, as well as those for the Marcus Institute, are under the IO’s supervision. The IO is responsible for:

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

2.1 Research Activities Reviewed by the HSL IRB

A variety of human research activities are conducted at HSL and by HSL Investigators, including:
- Social, behavioral, and educational research;
- Biomedical research;
- FDA-regulated research, including research involving drugs that require an IND and devices that require an IDE.

2.2 Research Activities for Which the HSL IRB Will not Normally Provide Review

Based on the typical patient population at HSL and nature of the research conducted at HSL and by its Investigators, and given the baseline composition expectations for the HSL IRB, the following categories of research will not normally be reviewed by the HSL IRB absent special circumstances and preparation:
1. Research involving a waiver of consent for planned emergency research;
2. Activities (both research and treatment protocols) involving humanitarian use devices;
3. Research that plans to or is likely to involve prisoners as participants;
4. Research involving children as participants;
5. Research involving pregnant women, fetuses, or neonates as participants;
6. Research using Broad Consent under 45CFR46.116(d);
7. Research using limited IRB Review under 45CFR46.104(d)(7-8)

While the HSL IRB does not ordinarily review the above-noted research, with advanced-notice by an HSL Investigator the IRB Director may be able to arrange to review or cede review of a specific protocol or category of research in items 1-7 (above) to another institution with an IRB that is appropriately constituted to review such research activities. For more information on Ceded Review, see Section 5.8.

2.3 Responsibilities of the IRB

The responsibilities of the IRB include reviewing and overseeing research activities at HSL or conducted by HSL Investigators in a manner that is compliant with applicable federal and state regulations, institutional policies, and ethical guidelines for the protection of human participants. The IRB should ascertain the acceptability of proposed research in relation to institutional commitments, applicable laws and standards of professional conduct and practice. This includes the following activities, which are outlined in more detail throughout this policy document:
- Determining whether a proposed activity meets the definition of ‘Research’ or research involving ‘Human Subjects’;
- Determining whether any proposed Human Subjects Research is exempt from IRB review and oversight and informed consent pursuant to 45 CFR 46 and 21 CFR 56;
- Except when an expedited review procedure is used in accordance with regulatory requirements, reviewing proposed research at convened meetings at which a majority of the HSL IRB members are present, including at least one member whose primary concerns are in nonscientific areas;
- Conducting reviews of initial and continuing research, proposed changes to approved research, unanticipated problems involving risks to research participants or others, and allegations of serious or continuing noncompliance with applicable regulations, policies or the requirements of the IRB;
- Reporting IRB findings and actions to the Investigator, and to the Institution, granting agencies and federal and state authorities when appropriate;
• Determining which projects require review more often than annually and which projects need verification from sources other than the Investigators that no material changes have occurred since the last review.

2.4 IRB Composition

Per regulations at 45 CFR 46.107, the HSL IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the Institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects. The HSL IRB includes members who have specific knowledge and experience working with adults with impaired decision making capacity, which is a population typical in the type of research it reviews.

Additionally:

• The IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

• The IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

• No IRB may have a member participate in the IRB’s initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

• An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

2.5 IRB Chair Requirements

Appointment: The IRB Chair is appointed by the Institutional Official, with input from the Director of the Marcus Institute & Vice President for Academic Medicine, the Director of IRB Operations, the General Counsel and Chief Compliance Officer, and if the proposed Chair is from an HSL department, the Head of the Department in which that person is a staff member. B. During any period of temporary vacancy, the Institutional Official may appoint an interim or acting Chair with input from these same individuals. The term of service for the IRB Chair is three years, with re-appointment possible; there is no term limitation.

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

**Evaluation:** An evaluation of performance of Chair duties and responsibilities will ordinarily be conducted each year by the Institutional Official to coincide with the date of appointment.

**Responsibilities:**
- Ensuring compliance of IRB actions with federal and state laws, institutional policies, ethical guidelines, and the terms of HSL’s FWA, where applicable;
- Presiding over the majority of convened IRB meetings, allowing sufficient time and opportunity for members present to discuss and vote on the studies under review, and to provide clarification and leadership for members;
- Providing or arranging for educational presentations and/or materials for the IRB members regarding new developments in applicable laws, policies, ethical guidelines or public affairs;
- Identifying when additional expertise beyond that represented by the IRB membership would be necessary or useful in the review of a particular protocol and arranging for an ad hoc consultant to the IRB or other resources as appropriate;
- When necessary, communicating with the IO, IRB Staff, IRB members and/or Principal Investigators when there are issues with the review of research, or the design and/or conduct of research;
- Constituting sub-committees of the IRB as appropriate to address specific issues, including the investigation of subject complaints or allegations of non-compliance;
- Participating in the development and approval of IRB policies and procedures, and other materials to be used as resources for Investigators and IRB members.

### 2.6 IRB Member & Alternate Requirements

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

**Training:** In addition to the requirements of 45 CFR 45.107 (see section 2.4), HSL IRB members must successfully complete CITI training in human subjects protection every three years, and attend other trainings as requested or required by the Institutional Official or IRB Director. Each new IRB member has access to the HSL IRB Policies and Procedures, relevant DHHS and FDA regulations, commonly referenced OHRP guidance, as well as a copy of the Belmont Report. In addition to these materials, any updated regulations, education and policy materials are circulated with the monthly meeting packets and reviewed at convened IRB meetings.

**Alternates:** Designated alternate members are appointed to the IRB and ordinarily have similar qualifications as the primary IRB member with whom they alternate. Alternate members are selected by the IO upon the recommendation of the Chair, IRB Director, and/or current IRB members. Alternate members are asked to serve for a minimum of three years, co-terminus with the primary IRB member with whom they alternate, however there is no term limitation. Alternate members are called upon to attend meetings when the primary member cannot attend; they are provided with the same materials as primary members.

**Evaluation:** IRB members are evaluated on their attendance, performance and participation in convened meetings (including subcommittee meetings), and as primary and secondary reviewers of research.
2.7 **Use of Consultants**

If a study under review involves a population or topic area that is not within the expertise of the membership at that time, the IRB Director will discuss with the Chair and the IO whether a consultant with such expertise should be retained. IRB members, HSL faculty and other local IRBs may be asked to suggest individuals with knowledge and competence in the topic area. Consultants may be used to provide specific content information to the IRB, but these individuals are not IRB members and therefore not permitted to vote.

2.8 **IRB Administration**

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

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

All IRB staff must complete training in human research protection through CITI upon employment, and certification must not be more than three years old. IRB staff who are responsible for IRB Operations (e.g. development of policies, procedures, review processes, etc.) and who analyze research protocols should be Certified IRB Professionals (CIP) upon hire or within 6 months of hire, and recertification shall be ongoing every three years. IRB Staff may attend local and national conferences and workshops on human subject protection issues.

2.9 **IRB Member Confidentiality**

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

2.10 **IRB Member Conflicts of Interest**

All IRB members with a possible conflict of interest (COI) must identify the conflict prior to review of the impacted research and recuse themselves from the review, if appropriate. A COI is considered to exist where an IRB member’s own professional, personal or financial interests (as further explained below) may reasonably be found to directly and significantly impact the member’s review of the research, whether positively or negatively. No IRB member with a COI will be allowed to provide a review, a determination,
or a vote on research with which they have an actual or perceived conflict. This policy is applicable to consultants who may be engaged to review research activities, and IRB staff who may conduct research determinations as outlined in Section 5.3.

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

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

**Professional conflicts of interest** arise when, for example, an IRB member has a supervisory/mentoring role over someone on the research team; is supervised/mentored by someone on the research team; has a role in the study (such as a co-Investigator or collaborator); is a member of a board supporting the study; or may suffer a professional loss, such as standing in the professional community if the study is or is not approved. IRB members who are colleagues in the same department of an Investigator whose research is under review are not necessarily considered to have a professional conflict of interest. Such members should use their discretion on whether they may feel bias or pressure to approve or disapprove the research.

**Personal conflicts of interest** arise when, for example, an IRB member is the spouse, partner or relative of an Investigator on the study under review, or has some other type of personal history with an Investigator on the study that would bias or would be perceived as biasing the IRB member’s review of the research.

**Financial conflicts of interest** arise when, for example, an IRB member or his or her family member (defined here as a spouse, domestic partner, and dependent children) has any financial interest in the study under review, including the potential for financial gains or losses through payments or consulting fees, equity interest or intellectual property rights from the research study or its sponsor or in the design, conduct, or reporting of the research. Proprietary interest related to the research includes, but is not limited to, a patent, trademark, copyright or licensing agreement. While it is possible for financial conflicts held by Investigators to be managed under the HSL Conflicts of Interest Policy, IRB members must recuse themselves from reviewing any study in which they have any financial conflict, as defined above.

2.11 **Indemnification**

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

2.12 **Meeting Schedule**

The HSL IRB is scheduled to meet on the third Monday of every month. On occasion, meetings are held on different days and times, depending on holiday or quorum issues, or extenuating circumstances. “Emergency” meetings are not ordinarily called unless safety issues or significant regulatory issues have been identified with a study or Investigator. Subcommittee meetings are held on an ad hoc basis, depending on necessity. When there are no protocols to review and no educational trainings to conduct, meetings may be cancelled.
2.13 Quorum Requirements

Quorum requirements are the majority of the IRB, inclusive of at least one non-scientific member (i.e. if the membership is 8, then the quorum is 5, and if the membership is 9, then the quorum is 5). IRB members are encouraged to attend all convened meetings (for reasons such as last minute quorum issues, scientific expertise, experience with previous reviews of a study, and familiarity of studies conducted by an Investigator). If quorum is not attained or is lost during the meeting, no actions may be taken by the IRB until the quorum exists or is restored. IRB staff are responsible for ensuring quorum for the convened meetings, and during the meetings. Approval of research requires a vote to ‘approve’ by a majority of IRB members present (including those who may be participating by phone) at a convened meeting.

2.14 Review System

The HSL IRB uses a primary reviewer system. Primary reviewers (herein referred to as ‘Reviewers’) conduct thorough reviews of studies proposed for initial and continuing review, as well as modifications to previously approved research, and present their review and recommendation to the full board at a convened meeting as further described below. The IRB Chair ordinarily serves as the Reviewer for reported unanticipated problems involving risks to participants or others, and allegations of serious or continuing non-compliance.

Reviewers are ordinarily selected by the IRB Director and/or Chair. Whenever possible, Reviewers will have expertise appropriate to the review of the assigned study. If this is not possible, or if the Reviewer does not believe that s/he has the appropriate expertise, the Director will arrange for another member to review the protocol, seek a consult, or defer the review until appropriate expertise has been secured. Secondary reviewers are often asked to provide additional review. The secondary reviewer is chosen to present the study if the primary reviewer is unable to attend the meeting, or if the issues presented in the study are unusually complex. The secondary reviewer may have additional expertise relevant to the study, or may be a new IRB member added as a Reviewer to gain experience.

Reviewers are responsible for conducting a thorough evaluation of all protocol materials submitted by the Investigator, and any additional materials for reference provided by the IRB Staff. In general, protocol review materials should provide sufficient detail to permit the IRB to make an informed judgment about whether to approve a study. Where the submission requires more information, the Reviewer may either ask the IRB staff to request this information from the Investigator, or contact the Investigator directly. The Reviewer is responsible for presenting the research proposal at the convened meeting, including raising any issues or questions, and his/her recommendation for approval.

2.15 Approval Criteria

In accordance with criteria at 45CFR46.111:
(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:
(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained
in the research (for example, the possible effects of the research on public policy) as among those
research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the
purposes of the research and the setting in which the research will be conducted and should be
particularly cognizant of the special problems of research that involves a category of subjects who
are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired
decision-making capacity, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized
representative, in accordance with, and to the extent required by 45 CFR 46.116 and when applicable,
21 CFR 50.20.

(5) Informed consent will be appropriately documented or appropriately waived, in accordance with, and
to the extent required by 45 CFR 46.117 and when applicable, 21 CFR 50.27.

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

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

(8) For the purposes of conducting the limited IRB review as required by 45 CFR 46.104(d)(7), the IRB
need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the
following determinations: (i) Broad consent for the storage, maintenance, and secondary research use
of identifiable private information or identifiable biospecimens is obtained in accordance with the
requirements of 46 CFR 46.116(a)(1)-(4), (a)(6), and (d); (ii) Broad consent is appropriately
documented or waiver of documentation is appropriate, in accordance with 45 CFR 46.117; and (iii)
If there is a change made for research purposes in the way the identifiable private information or
identifiable biospecimens are stored or maintained, there are adequate provisions to protect the
privacy of subjects and to maintain the confidentiality of data. Note: because HSL does not offer the
use of Broad Consent at this time, items 8(i)-(ii) above do not apply to HSL Investigators.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as
children, prisoners, individuals with impaired decision-making capacity, or economically or
educationally disadvantaged persons, additional safeguards have been included in the study to protect
the rights and welfare of these subjects.

2.15.1 Scientific Review

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

Under the Revised Common Rule, effective January 19, 2019, IRBs are not required to review DHHS funding applications supporting research with human subjects. Instead, certification is required when the research is supported by a federal department/agency and not otherwise waived under 45 CFR 46.101(i) or exempted under 45 CFR 46.10. For such research, HSL shall certify that each proposed research study covered by the Assurance has been reviewed and approved by the IRB. The exception to this rule include specific DHHS/NIH policy requirements for certifications of grant concordance with the research protocol and/or the informed consent of original study participants for Genome-Wide Association Studies (GWAS), Genomic Data Sharing Plans (GDS), and other studies requiring such certification.

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

Federal regulations at 45CFR46.122 stipulate that no federal funds may be expended for human subjects research unless the requirements of the regulations have been met. Principal Investigators may access research funds to conduct human subjects research once they have provided the Grants Office with evidence of current and relevant HSL IRB approval. HSL is aware that certain types of grants, contracts, and agreements are applied for and awarded with no definite plans for the involvement of human subjects. These may include institutional awards (where the selection of projects to fund is the institution’s responsibility), training grants (activities involving human subjects are not yet selected), and projects that will not enroll human subjects until the completion of instruments, prior animal studies, etc. Under 45CFR46.118, the IRB is not required to review such applications prior to the Investigator receiving the funds, however no human subjects research may occur until the project has been reviewed and approved by the IRB. Under 45CFR46.119, grants that are awarded without the intent to involve human subjects, but later propose to involve human subjects, should be submitted for IRB review prior to the enrollment of human subjects.

2.15.3 Off-site Research

IRB members should be qualified to understand the particular risks and benefits of the impacted study population, and the relevance, customs and cultural significance of study procedures to the community in which the research is taking place. If this is not possible, a consultant with the appropriate expertise may be asked to review the research and to provide input to the IRB.

When DHHS is supporting the research, each local site (whether domestic or international) ordinarily must have a FederalWide Assurance and approve the research prior to implementation, or execute an Individual Investigator Agreement as outlined in Section 3.4, as appropriate. In the event that non-federal (or no) funds are supporting the research, IRB or Ethics Committee approval may still be required at each research site, unless there is no such reviewing authority where the research is taking place. While some communities may not have an official review board, there may be an existing infrastructure (council or local leader) that approves the activities of the community. If no such infrastructure exists, a letter of support from the local site (such as a school principal or superintendent, or a clinic director) where the research activities will be taking place should be obtained by the Investigator and provided to the HSL IRB. The letter should include information pertaining to the appropriateness of the study to the local community, any required changes to the study, and a review and approval of the consent document, whenever possible. Letters not provided in English should be translated into English by the PI, or someone hired by the PI, for HSL IRB review and a signed Translation Attestation Form must accompany the letter.
2.16 Approval Decisions of the Convened IRB

In exercising its decision-making authority, including to approve, require modifications to secure approval, or disapprove all research activities involving human research participants overseen and conducted by HSL (see Section 1.1), IRB members may make the following motions with respect to any matter requiring a vote by the convened IRB: those in favor, against, or abstaining from a vote. In order for a motion to pass, it must be voted for by a majority of the meeting quorum. Abstaining votes count towards the quorum, however IRB members who have declared a conflict of interest cannot vote (and are not present for the discussion or vote) and therefore are not counted towards the quorum for that vote.

2.16.1 Approval

Approval means that all aspects of the study have been reviewed and found to be scientifically, methodologically, and ethically sound, and to meet regulatory criteria for approval (see Section 2.14). Research requiring continuing approval will maintain the annual date of approval, as long as the research is re-approved within 30 days prior to the expiration date. An approval letter will be sent to the Investigator by IRB staff ordinarily within 5 business days of the IRB meeting. It is the responsibility of the Investigator to forward approval notices received from the IRB to Sponsors or others who may need a copy of the notice.

2.16.2 Conditional Approval

Conditional Approval means that the study requires only specific minor revisions or yes/no concurrence by the Investigator to meet regulatory criteria for approval.

Specific minor revisions may include changes to study materials, study procedures, or other changes that do not alter the risk and benefit analysis of the study. Minor revisions cannot affect the safety of participants, or alter in any way the scientific integrity of the study, or include a procedure for which expedited review is not permissible.

Procedures for conditional approval are as follows:

- A letter or email outlining the conditions, and any response timelines, will be sent to the Investigator by IRB staff ordinarily within 5 business days of the convened meeting.
- If a continuing renewal receives conditional approval, the IRB may need to determine if research may continue while the conditions are addressed, or if research activities must stop until the Investigator’s response is found to adequately address the conditions. If the IRB decides that the research should stop, it will issue a deferral as outlined in Section 2.15.3.
- Investigator responses to conditional approvals, including any revised materials, will be sent to the Chair and Primary Reviewers for review, and may be fully approved only after the Reviewers confirm that the conditions for approval have been satisfied.
- If the concurred/revised materials are satisfactory, a letter indicating IRB approval will be sent to the Investigator by IRB staff. Note:
  - If conditional approval is granted at initial review, the effective date of approval (and the first date by which continuing review must occur) will be the date that the Chair and/or Primary Reviewers determine that the conditions of approval have been satisfied, unless otherwise specified by the IRB.
  - When conditional approval is granted on continuing review, the effective date of approval will be the same fixed annual date, as long as the conditional approval is granted within 30 days prior to the expiration date (whether or not the conditions are met by that date).
• When, in the opinion of the Chair and/or Primary Reviewer(s), an Investigator fails to meet the conditions, the IRB will reconsider the matter at the next convened meeting.
• Investigators who disagree with the conditions may address the convened IRB in person or in writing.

2.16.3 Deferred Approval

Deferred approval means that the study does not meet the criteria for approval or requires more than specific minor revisions or modifications in order to be approved. Procedures for deferred approval are as follows:

• A letter or email including the reasons for the IRB’s decision and any IRB suggestions or stipulations will be sent to the Investigator by IRB staff ordinarily within 5 business days of the convened meeting.
• Studies that are reviewed by the convened IRB and are deferred must be reviewed, once revised, by the convened IRB. The study is subject to the approval criteria outlined in Section 2.14.
• Revised materials should be resubmitted to the IRB within six months of deferral, unless the issue delaying the submission is not within the Investigator’s control, such as device or drug approvals from the FDA. If the stipulated modifications are not resubmitted within six months of the deferral, the IRB office will contact the Investigator to determine whether the study should be closed. If no information is forthcoming, the IRB office may decide to close the file and will notify the Investigator in writing of its decision. Investigators may be required to submit new applications following the closure of a file.

2.16.4 Disapproved

‘Disapproved’ means that the study is not scientifically, methodologically, and/or ethically sound, and does not meet regulatory criteria for approval; as such the IRB will not approve the study as designed. A disapproval letter will be sent to the Investigator by IRB staff ordinarily within 5 business days of the meeting, and shall include the basis for the disapproval and provide an opportunity for the Investigator to address the convened IRB in person or in writing regarding its action. Investigators may resubmit protocols that have been disapproved after significant revisions have been made to address the stated deficiencies.

2.17 Research Requiring Review More Often than Annually

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

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

When the IRB has determined that more frequent than annual review is warranted, it will document its determination in the minutes of the meeting. IRB staff will communicate the determination in writing (as well as the rational for the decision) to Investigators within 5 days of review.
2.18 Research and Consent Monitoring

The IRB has the authority to ‘observe or have a third party observe the consent process and the research’. Observations are ordinarily requested by the convened IRB, and may be requested for a variety of reasons (e.g. a complicated research project is being conducted by a new Investigator, the consent form is lengthy and includes numerous procedures or risks, complaints have been received about the research or research staff, a member of the research team has an identified a related conflict of interest, etc.). The convened IRB will determine the appropriate observers, who could include: the IRB Chair, IRB members, IRB staff, HSL faculty, staff or administration, third parties with experience in the research topic or procedures, or third parties with experience in research monitoring. Determinations to conduct observations of the consent process and/or the research will be documented in the minutes of the meeting. IRB staff will communicate the determination in writing to Investigators within 5 days of review.

2.19 IRB Fees for Review of Research

Due to the resources required to review industry-sponsored research and that such research is provided as a service to the industry sponsor through a sponsored research or clinical trial agreement, HSL will invoice industry-sponsors for review by the HSL IRB. The below fees are charged regardless of whether a protocol receives approval. The fee for initial review of research will be taken either from the first check received from the sponsor or billed separately, depending on the terms of the contract. Subsequent fees will be charged to the account or billed directly, as they are incurred.

Fee Schedule:

<table>
<thead>
<tr>
<th>Description</th>
<th>Fee</th>
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<tbody>
<tr>
<td>Initial review of protocol and associated material</td>
<td>$2000</td>
</tr>
<tr>
<td>Major amendment to protocol (requiring convened board review)</td>
<td>$500</td>
</tr>
<tr>
<td>Continuing review (required at least annually)</td>
<td>$1000</td>
</tr>
</tbody>
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In accordance with 45 CFR 46.114, institutions in the United States engaged in cooperative research projects must rely upon the approval of a single IRB. When HSL is chosen to be the IRB of record, it may require the relying sites to pay the above-noted fees for any ancillary studies they may choose to initiate and that require the review of the HSL IRB.

2.20 Documentation

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

1. Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by Investigators, and reports of injuries to subjects.
2. Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution (see Section 2.19.2).
3. Records of continuing review activities, including after January 18, 2019, the rationale for conducting continuing review of research that otherwise would not require continuing review under the Revised Common Rule at 45 CFR 46.109(f)(1).
4. Copies of all correspondence between the IRB and the Investigators.
5. A list of IRB members in the same detail as described in 45 CFR 46.108(a)(2).
6. Written procedures for the IRB in the same detail as described in 45 CFR 46.108(a)(3) and (4).
7. Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5).
(8) The rationale for an expedited reviewer’s determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in §.110(a) is more than minimal risk.

(9) Documentation in the form of this policy and procedure manual specifying the responsibilities that HSL will undertake to ensure compliance with the requirements of this policy under § .103(e).

Record retention policies are outlined in Sections 2.19.4 and 2.19.5. All records shall be accessible for inspection and copying by authorized representatives of the relevant department or agency with jurisdiction over the research at reasonable times and in a reasonable manner.

2.20.1 IRB Meeting Materials

IRB meeting materials are ordinarily available to IRB members via the electronic IRB (eIRB) system seven days prior to the convened meeting to allow sufficient time for review, and to request additional information before the meeting, if necessary. Primary, Secondary Reviewers and IRB members are able to view the same materials for review. For ‘Legacy’ studies (those that existed prior to the implementation of the eIRB system in July 2016), protocol files containing the complete history of the studies under review are brought to and referenced during the meeting. Protocols initially submitted via the eIRB system are available in their entirety (all reviews and review materials) in the eIRB system.

Complete meeting packets for convened IRB meetings that occurred prior to the implementation of the eIRB system are maintained on the IRB shared drive. Complete copies of meeting materials since the implementation of the eIRB system are maintained and available in the system.

2.20.2 IRB Meeting Minutes

Minutes of the IRB meetings, in compliance with 45 CFR 46.115(a)(2), include:

- The names of all IRB members present, and the names of any alternates and the IRB member they are replacing;
- The names of all non-members present;
- Date of meeting;
- Time the meeting commenced and concluded, and the time of any members entering or leaving the room after the meeting has begun;
- The names of the members who absent or recuse themselves from the meeting due to a conflict of interest (including the time of recusal and the time of return to the meeting, if applicable), along with the identification that a conflicting interest is the reason for the absence/recusal.
- Documentation of each project under review, including:
  - PI name, project title, HSL protocol number, and review status (e.g. initial, continuing, amendment, adverse/unexpected event, non-compliance);
  - A written summary of the discussion, including any controverted issues and their resolution;
  - Any questions or suggestions for the Investigator that do and do not have bearing on the approval of the study;
  - Any required changes to the study and the basis for requiring those changes;
  - Separate deliberations for each action requiring review (e.g. continuing review, amendment);
  - Determinations required by the regulations and protocol-specific findings justifying those determinations for certain IRB actions and/or categories of research if applicable (e.g. waiver or alteration of the consent process; any special criteria required under Massachusetts law; the rationale for significant and non-significant risk device determinations, etc.).
  - The basis for disapproval of research, as applicable;
  - Approval period for initial and continuing reviews;
  - A record of votes for, against, and abstaining from approving the research;
Meeting minutes are ordinarily available to IRB members through the eIRB system. The minutes are reviewed and voted upon ordinarily at the next convened meeting (e.g. June minutes are sent with the July meeting packet and accepted at the July meeting). A copy of the approved/accepted minutes are kept in the ‘Minutes’ folder on the IRB shared-drive, and maintained in perpetuity.

2.20.3 Membership Rosters

IRB membership rosters contain the members’: name, professional degrees, affiliation or non-affiliation with HSL, scientific or non-scientific status, mailing address, office and/or mobile phone number, email address, and designation as a primary or alternate member. Rosters are modified as changes are made, and final versions are maintained on the IRB shared drive. All changes in membership are approved by the HSL Institutional Official (IO). Paper copies are available from the IRB staff, and made available to anyone who requests the information. IRB Rosters are on-file with the IO, the General Counsel and Chief Compliance Officer, and the CEO/President’s Office.

2.20.4 Active Study Files

Study files for active and ongoing projects that have received expedited or convened IRB approval are maintained in the eIRB system, and for Legacy Projects, in a locked file cabinet located in the Marcus Institute. The files are organized such that the IRB or others could construct a history of the study and the IRB actions pertaining to the review and approval of the study. The files contain the documentation required for IRB review and approval, as well as the documentation sent to the PI, and received from the PI or the research staff.

All Legacy records pertaining to a study are be kept together in the file cabinet until the study is closed. Minutes of convened IRB meetings are stored separately.

Exempt research and studies not meeting the definition of research or research with human subjects that were Legacy projects were scanned in their entirety; a pdf was created and the materials are stored on the IRB shared-drive (listed by Investigator last name and protocol number). The original paper copies are stored in HSL archives and maintained according to the record retention policy outlined in Section 14.3.

2.20.5 Inactive Study Files

The IRB maintains all study records, beyond the criteria at 45 CFR 46.115(b), for seven years after the final report is submitted to the Sponsor, or until the date specified by the Sponsor. If there is no Sponsor, the records are maintained for seven years after the study is closed by the PI or the IRB. The paper Legacy records are stored in archive boxes, listed by PI and chronological protocol number, and are stored in HSL archives and maintained according to the record retention policy outlined in Section 14.3. The IRB staff maintains a list of stored Legacy records.

2.20.6 Policies and Procedures

The IRB Policies and Procedures are developed and updated as necessary and posted in their entirety on the Marcus Institute website. Substantive changes to the policies are ordinarily reviewed and approved, as appropriate, by the IRB Director, IRB Chair, IO, General Counsel and Chief Compliance Officer and IRB members; minor changes (e.g. spelling, grammar, review processes) that do not alter a regulatory or Institutional policy, do not require review and approval. The policy document contains the most recent date of approval and a signature page addendum indicating approval by the IO, the General Counsel and Chief Compliance Officer and the Chair, on behalf of the IRB. Changes in regulations, policies or procedures that
require immediate action or significant effort on the part of the Investigators (or their staff) are sent via email to the affected parties, as appropriate, and corresponding changes to the policy document will be made and implemented as soon as possible.

2.20.7 IRB Applications and Forms

IRB Applications and Forms are developed and updated as necessary by the HSL IRB staff, and available through the eIRB system.

2.20.8 IRB Webpage

The HSL IRB Policies and Procedures, training requirements and helpful links may be found on the Marcus Institute webpage. New or revised materials for the website are provided by the IRB Director to the Marcus Institute website manager.
3. Investigator and Research Personnel Requirements

3.1 Principal Investigator

**Qualifications:** The Principal Investigator (PI) must have appropriate training, including both technical training and human subject protection training (see Section 3.7), and the necessary credentials and privileges to conduct the research. If the research involves interventions or interactions with study participants, the PI must ordinarily be a member of the HSL faculty and have a clinical or non-clinical staff appointment above the level of resident, fellow or student. When the research involves administration of a drug or implantation or use of a device, the PI or a Co-Investigator must be a licensed physician, with appropriate credentials and privileges at HSL or the institution where the clinical activities are taking place.

**Responsibilities:** PIs are responsible for conducting and supervising the research, and bear the primary responsibility for the protection of participants in their research studies. The responsibilities of the PI include:

- Adhering to the federal regulations, institutional policies, and ethical guidelines outlined in this policy document, as well as any other applicable federal or state laws or contractual obligations related to the conduct of a research project;
- Upholding the highest standards of ethical and professional conduct;
- Attending and completing periodic trainings required and/or sponsored by the IRB;
- Assuring appropriate training, education, credentialing and privileges of those co-Investigators and staff to whom the PI delegates responsibilities, and only delegating tasks where appropriate and indicated;
- Communicating with the IRB in a timely manner when questions or problems arise related to the research;
- Providing accurate and timely information to sponsoring or oversight agencies;
- Disclosing conflicts of interest;
- Receiving HSL IRB approval before commencing new research activities, and before implementing changes to approved research or research materials;
- Receiving timely continuing approval for all applicable research;
- Obtaining (and documenting) informed consent and HIPAA Authorization from all participants, unless the IRB has issued a waiver or alteration of either or both requirements;
- Ensuring privacy for study participants and confidentiality of study participant data;
- Reporting study incidents to the IRB and study sponsors as required by applicable law, institutional policies, the protocol and/or contractual agreement, such as: adverse events, unanticipated problems, violations or deviations from the approved protocol, suspensions or terminations of research, complaints about the research from study participants or others, and data safety monitoring reports, as applicable;
- Maintaining appropriate study records as required by federal, state and HSL policies and procedures;
- Billing research budgets, grants, sponsors and/or third party payors appropriately with respect to any research related items and services and cooperating with the institution in conducting any coverage analyses necessary for a given research project;
- Participating and cooperating in quality assurance reviews, investigations and other oversight and monitoring activities.

**For FDA regulated research,** the PI is the responsible team leader as defined by the term ‘Investigator’ in FDA regulations 21 CFR 312.3(b) and 21 CFR 812.3(i). Investigators who are also the regulatory ‘sponsor’ and hold an IND or IDE must complete Good Clinical Practice training.
Principal Investigator Leave of Absence, Sabbatical, Move to Another Institution, or Retirement:
Principal Investigators (PIs) are responsible for timely closure of studies or transfer of responsibilities in the event of an absence for medical or family leave, sabbatical, move to another institution, or retirement.

- In the event of a temporary absence (e.g. 8-week medical leave) where a complete return to duties is expected, a co-Investigator may assume interim PI responsibilities without a formal change of PI.
- In the event of a leave of absence for 3 months or longer, a qualified on-site PI must be formally appointed (note: this is also an NIH mandate), which requires IRB review and approval. The new PI must be willing to assume all PI responsibilities.
- In the event of any leave of absence or departure, the grant manager or VP for research administration will review the terms of any applicable sponsored research agreement to ensure compliance with any requirements for appointing a substitute or successor PI.
- When an Investigator leaves HSL (e.g. to move to another institution, or retirement) his/her original research records must be retained at HSL.
  - When an Investigator is moving to a new institution, an active protocol may be transferred to the new institution if the grant/contract and the responsibility for the review and oversight of the protocol also move to the new institution. In the case of an active protocol, the PI may take a copy of the research records in order to complete the protocol at the new institution, but any and all original research records developed or created at HSL must remain at HSL.
  - All research records at HSL will be maintained and destroyed according to the Marcus Institute Record Retention Policies.
  - Data and specimen repositories created at HSL using information and materials created, collected or received by employees of HSL are the property of HSL and will remain the property of HSL even following the departure from the institution of an Investigator or other employee who assisted in their creation. Investigators moving to new institutions must apply to HSL data repositories according to the approved process to use data for future research projects, notwithstanding prior involvement in the creation of the repository or the underlying research from which information and specimens were contributed to the repository.
  - Investigators leaving HSL may not remove research records, research data or research specimens from HSL without the express permission of Research Administration, Research Informatics, and/or the IRB, as appropriate.

The transfer of responsibilities (including those of the PI and the IRB review) should be completed before the PI leaves HSL. If a third party contract regarding research funding contains more stringent requirements with respect to transitions in researchers or institutions than what is included in this policy, those contractual requirements shall apply.

3.2 Co-Investigator

Co-Investigators ordinarily hold doctoral or other professional degrees and contribute to the scientific development or execution of a study in a substantive, measurable way. Co-Investigators at HSL must be qualified by training and experience and have any necessary HSL credentials and privileges to conduct the tasks delegated to them by the PI.

3.3 Research Personnel

HSL research personnel include the PI, co-Investigators, project directors, research nurses, data analysts, research coordinators, and research assistants. All HSL employees who intervene or interact with research participants or access identifiable private information of those participants for the purposes of the research, or who are responsible for the design, conduct, reporting of the research must be listed on a Personnel Roster.
Members of the HSL workforce whose association with a research project is limited to providing standard clinical services (e.g. pharmacy personnel, phlebotomists, therapists, patient care services) or routine clinical tests, making appointments, or performing other tasks that they would otherwise perform as part of their non-research responsibilities are not considered research personnel and should not be listed on a Personnel Roster.

Individuals who are involved in the research but do not intervene or interact with research participants or do not have access to identifiable private information about the research participants or who are not responsible for the design, conduct, reporting of the research should not be listed on the Personnel Roster. This may include individuals who receive a subcontract to provide consulting services related to the research, and those who may develop research materials or analyze de-identified data, presuming they meet the above criteria.

### 3.4 Non-HSL Personnel working on HSL Approved Research

HSL Investigators regularly collaborate with research personnel from other institutions. Unaffiliated research personnel engaged in research must fulfill obligations with their own institution’s IRB. Depending on the nature of the research and the responsibilities of the unaffiliated research personnel, their institution may require concurrent IRB review, may request to make arrangements for ceded review to the HSL IRB (see Section 5.6), or may determine that review is not required for their institution given the nature of the collaboration.

For federally sponsored research, unaffiliated research personnel who are employed at an institution without an FWA (e.g., private practice or contracted medical or research personnel) must complete an Individual Investigator Agreement (IIA) with HSL. This Agreement must be signed by the HSL Institutional Official, the un-affiliated research personnel, and the unaffiliated research personnel’s Institutional Official, if applicable. The HSL IRB Office maintains the IIA templates for completion, as well as the full executed (signed) Agreements.

If research activities by non-HSL personnel will be conducted at HSL facilities (including the housing sites) appropriate documentation must be completed with HSL Human Resources (HR) and Occupational Health. Investigators must confirm clearance with HR before non-HSL personnel may commence any research activities at HSL. Note: Occupational Health will not provide immunizations for non-HSL personnel therefore non-HSL personnel will need to provide immunization records from their own doctors to Occupational Health for clearance.

Unaffiliated personnel who will physically intervene with research participants (e.g. medical, nursing, physical therapy) must receive appropriate credentialing and permissions or privileges by the respective HSL departments (e.g. Medicine, Nursing) prior to commencing research activities.

### 3.5 Unaffiliated Investigator Research with HSL Residents

HSL residents and patients are welcome to participate in research that is of interest to them (presuming they meet appropriate inclusion criteria), whether it is research conducted by HSL Investigators, or Investigators who are unaffiliated with HSL.

Research conducted by unaffiliated, external Investigators with HSL residents/patients (including resident/patient information) or their family members generally falls into two categories:
1) Activities that engage HSL and its employees in the research:
For research initiated and managed by another institution (for which HSL may or may not receive a subcontract or agreement supporting the research) where HSL is a research site and its workforce members will be engaged in the research, a HSL site Investigator must be identified. The HSL site Investigator may be a HSL faculty member, or a member of the HSL senior staff.

If HSL is engaged in the research (see Section 5.2.3), the HSL IRB will either review the research or rely on the review of the reviewing IRB. The decision on whether to review or to rely is made on a case-by-case basis, and includes but is not limited to, whether the research falls under the NIH Single IRB Review policy, and whether the HSL IRB is more properly constituted to review the research proposed to be conducted with its residents.

Engagement in research includes activities such as: receiving a direct award from HHS, obtaining informed consent of research participants, collecting/receiving data or specimens that contain identifiable patient/participant information, interacting or intervening with participants/patients for research purposes.

In addition to IRB requirements, unaffiliated Investigators wishing to conduct research at HSL must obtain approval from any departments to be affected by the research (e.g. Department of Medicine, Physical Therapy, Nursing, Privacy Officer, etc.).

2) Activities that do not engage HSL and its employees in the research
For research initiated and managed by another institution where research activities take place at HSL and the role of HSL employees is limited to assistance with recruitment efforts, HSL is not considered engaged in the research, and therefore HSL IRB approval is not required.

Federal guidance on ‘Engagement of Institutions in Human Subjects Research’ can be found here.

Unaffiliated personnel who will physically intervene with HSL residents or patients (e.g. medical, nursing, physical therapy) at HSL facilities must receive appropriate credentialing, permissions or privileges by the respective HSL departments (e.g. Medicine, Nursing, Human Resources, Occupational Health, etc.) and housing sites prior to commencing research activities.

Performance sites that are legally separate from HSL are not authorized to cite the HSL FWA unless agreed to by HSL and documented through either an Individual Investigator Agreement or an IRB Authorization Agreement.

3.6 Investigator and Research Personnel Experience

Investigators must submit the Curriculum Vitae (CV) or Biosketches of all key personnel and research staff who are listed on the Personnel Roster and who will have responsibilities with study participants and/or data/specimens containing participant identifiers. CVs/biosketches are required in order to confirm that the Investigator and research staff have appropriate expertise to conduct the research and ultimately, protect the rights and welfare of study participants. If the IRB determines that an Investigator or a member of the research team is not qualified to conduct the study, it may request the appointment of a co-Investigator, consultant, or an appropriate mentor.
3.7 Required Trainings

Investigators, research staff, and others who are responsible for the design, conduct, or reporting of the research, have direct interactions with participants for research purposes (including obtaining informed consent), collect/receive/obtain identifiable research data/specimens, and those who have access to keys/codes with research subject identifiers are required to take applicable training, as identified below. Typically, individuals the PI has assigned study-specific roles and responsibilities (such as co-Investigators, research nurses, research coordinators, research assistants, etc.) are considered research personnel.

Members of the HSL workforce who provide standard clinical services (e.g. laboratory or radiology technologists, phlebotomists, physical therapists, nurses, etc.) as part of their HSL-designated, non-research responsibilities are not considered research personnel. As such, as long as these individuals will be conducting the same services/practices that they conduct in their day-to-day jobs, these individuals would not ordinarily be required to complete the following trainings.

- **Human Subject Protection:**
  The HSL Human Subject Protection Training (HSPT) curriculum is available through the Collaborative Institutional Training Initiative (CITI) Program. The HSPT is valid for a three year period, after which time a refresher training is required. IRB approval may only be granted when Investigators have current HSPT.

- **Conflicts of Interest:**
  Investigators and research staff are required to complete Conflicts of Interest (COI) training prior to engaging in Sponsored Research. The COI training curriculum is available online through the Collaborative Institutional Training Initiative (CITI). Training in COI is required every four years.

- **Good Clinical Practice:**
  NIH-funded Investigators and clinical trial site staff who are responsible for the conduct, management and oversight of NIH-funded clinical trials are required to take Good Clinical Practice (GCP) training. GCP training is available on numerous sites accepted by HSL, including CITI, the NIH Office of Behavioral and Social Sciences Research, or the National Institute of Allergy and Infectious Disease GCP Learning Center website.

- **Information Privacy and Security**
  The Marcus Institute requires its staff to take Information, Privacy and Security training, available through CITI. The training is required every three years and covers topics relevant to the HIPAA Privacy Act, and maintaining the safety and security of research data. This training covers topics specific to research and is in addition to the required BASICS training for HSL employees.

- **Responsible Conduct of Research:**
  The purpose of Responsible Conduct of Research (RCR) training is to promote principles surrounding ethical conduct of research, and set such expectations of our Investigators and Trainees. Recipients of certain National Science Foundation (NSF) and National Institutes of Health (NIH) Research Training Grants, Individual Fellowship Awards, Career Development Awards (Institutional and Individual), Research Education Grants, Dissertation Research Grants, and other grant programs include a training component that requires instruction in RCR. The Marcus Institute Policy on RCR can be found on its website, and online RCR training is available via CITI.
In addition to the online trainings, HSL offers, and at times may require, in-person training on human subjects research topics. The IRB Director and Chair are available to conduct trainings or to talk with Investigators and staff about topics relevant to their research.

3.8 Investigator Conflicts of Interest

All HSL Investigators and Research Staff must comply with the Hebrew SeniorLife Policy on Financial Conflicts of Interest in Sponsored Research as well as Department of Health and Human Services regulations at 42 CFR Part 50 Subpart F regarding conflicts of interest (COI). The HSL Policy requirements are in addition to the rules set forth in the Harvard Faculty of Medicine Policy on Conflicts of Interest and Commitments, which apply to HSL employees who also have appointments to Harvard Medical School.

When a Financial Conflict of Interest (FCOI) is identified by the HSL Research Compliance Committee, the IRB will review the conflict and the Management Plan to ensure that appropriate measures are taken to protect research subjects, and appropriately manage, reduce or eliminate the FCOI. The range of potential IRB actions may include the following, as well as other actions determined by the IRB at the time of review:

- No action.
- Notification to Research Subjects of the COI.
- Change in Investigator or Research staff role in the project.
- Removal of the Investigator or Research Staff from the research project.
- Suspension of the research project until the COI is resolved.
- Termination of the research project.
4. **Recruitment and Informed Consent Guidelines**

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

4.1 **Recruitment Guidelines**

Recruitment for participation in research studies takes many forms, including identification of potentially eligible subjects through medical record review, patient databases or registries, treating clinicians, family members or friends, and communication with potential subjects in the form of advertisements through media (e.g. print, radio, television, Internet), mass or targeted mailing (or emailing) campaigns, public posters and billboards, leaflets and other brochures made available in various locations such as community centers or private physician offices, etc. The IRB must ensure that recruitment methods are not coercive, do not promise what they cannot deliver (for example, the promise of treatment or cure in the context of a research procedure), and maintain the confidentiality and privacy of potential participants.

4.1.1 **Recruitment Plans**

Recruitment Plans outlined in the study protocol should include the following information:

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

4.1.2 **Recruitment Materials**

Recruitment materials to be seen or heard by potential research participants must be approved by the IRB. This includes all advertisements, scripts, mailings, websites, etc., before they are publicized or circulated in any way.

**General advertisements** about the study (e.g. fliers, posters, newspaper ads, websites, etc.) should include the following information:

- Name of the research project;
- Purpose of the project;
- Inclusion and any special exclusion criteria (e.g. smoker/non-smoker, age range, medical or social condition);
- Duration of participation;
- Name and contact information of research personnel for questions, or to participate.

**Direct Contact** with potential participants should include the above information for general advertisements, in addition to the following:

- How the Investigator received the potential participant’s name and contact information;
- Opt in or opt out information:
o Opt in – participants receive a letter about the study, which includes a phone number to call or a post card to return if they are interested in participating or learning more about the study. The Investigator does not call potential participants if they do not indicate by letter or phone that they wish to participate or receive more information;

- Opt-out - participants receive a letter about the study, which includes a phone number to call or post card to return if they are not interested in being contacted about participating or learning more about the study. Not opting-out by a certain date indicates to the Investigator that they can proceed with contacting the individuals.

- Letters should be signed by the Investigator and/or the treating clinician, as applicable.

Recruitment materials should not:
- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
- Highlight the potential benefits (e.g. larger or bold type) as opposed to potential risks;
- Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for purposes under investigation;
- Make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic or device;
- Use terms, such as “new treatment”, “new medication”, or “new drug” without explaining that the test article is investigational;
- Promise “free medical treatment”, when the intent is only to say participants will not be charged to take part in the study;
- Include exculpatory language (i.e. suggesting the Investigators or institution disclaim liability for the conduct of the study, or that participants waive legal rights by participating);
- Emphasize remuneration for participation (e.g. larger or bold type).

4.1.3 Review of Protected Health Information to Identify and Recruit Potential Research Participants

In order to use or disclose protected health information (PHI) for recruitment purposes, Investigators and their research staff must have a basis for both (i) screening patients' health information to identify potential research participants and (ii) contacting patients about possibly enrolling in the research study, as outlined in Section 11.7.

Treating physicians and other members of a patient’s treatment team are permitted to review their own patients’ health information to determine whether they might be eligible to enroll in a research study and to contact their patients about and/or discuss with their patients available research options.

If an Investigator is not a member of the patient's treatment team and wishes to review and use PHI for recruitment purposes, the Investigator should apply to the HSL IRB for a "partial" waiver of authorization. Such requests will be reviewed and evaluated in accordance with Section 11.4. Depending on the type of research being conducted, the IRB may require that the initial contact with the potential subject be made by a treating physician or other staff member with an existing relationship with the patient.

For research funded by the NIH and/or approved on or after January 21, 2019, the Revised Common Rule removes the requirement for partial waivers of consent for the use of information or specimens for the purposes of screening, recruiting, or determining the eligibility of prospective subjects for inclusion in the research. Pursuant to the Revised Rule, the HSL IRB may approve a research proposal in which an Investigator will obtain information or biospecimens for these purposes without the informed consent of
the prospective subject or the subject’s legally authorized representative (LAR) if either of the following conditions is met:

1. The Investigator will obtain information through oral or written communication with the prospective subject or LAR, or
2. The Investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

When research is subject to the Revised Common Rule, and either of the above conditions is met, Investigators do not have to request waivers of consent for the purposes of screening, recruiting, or determining eligibility but do have to describe the activities in the application or protocol submitted to the IRB. The above does not negate the requirements of other rules, such as HIPAA, when applicable. It also does not negate the requirement to obtain consent, or a waiver of consent, before involving a subject (including the use of their identifiable private information or biospecimens) in other research activities.

4.2 Remuneration Guidelines

Remuneration, also known as payments or compensation, to individuals who participate in research is ordinarily offered as a form of appreciation for the individual’s time and effort in the research project. Remuneration is not considered to be a “benefit” of participating in research. The IRB reviews remuneration plans to assess whether the amount, schedule and type of any proposed compensation is fair for the participant, and to assess whether the payments could be considered coercive (i.e. by unduly inducing individuals to participate because the compensation offered would be difficult to refuse). In general, remuneration:

- Should be comparable to other projects involving similar time, effort, and inconvenience;
- Should be pro-rated based on the number of procedures and study visits and should not be conditioned on completing the entire study, although a bonus for completing the study may be acceptable. Any amount paid as a bonus for completion must be reasonable and not so large as to unduly induce participants to stay in the study who would otherwise have withdrawn;
- Should ensure that participants’ confidentiality is protected and paid in a manner that allows them to retain privacy to the extent legally possible;
- Must not include “finder fees” (payment for referrals of prospective participants);
- Must not include a coupon from a trial sponsor for a discount on the purchase price of the product once it has been approved for marketing;
- Specifics (including the amount per visit and payment schedule) should be documented in the consent form under the “Compensation” section— but not under the “Benefits” section.

Investigators should note that aggregated remuneration by HSL to a United States citizen or permanent resident totaling $600 or more per calendar year requires reporting by HSL to the IRS on a Form 1099. For that reason, any participant who will receive a one-time payment (including gift cards) in excess of $50 or whom the Investigator has reason to believe is enrolled or plans to enroll in multiple studies where the total would exceed $600, must provide his or her Social Security Number (SSN) or Individual Tax Identification Number (ITIN) prior to participation, which must be protected by Investigators as confidential and sensitive information. Investigators should check with Research Administration (e.g. grant manager) when considering any payments or in the event they expect to enroll non-resident foreign nationals in a study in order to understand the implications for the participants, as well as the research team and financial operations group who may be processing the payments. The IRS does not require HSL to report to the IRS payments totaling less than $600 to one individual in a given calendar year; however, research participants may still need to report such payments on their individual income tax returns. Participants should be informed of any planned remuneration, the requirement to provide a SSN/ITIN, if applicable, and how that information will be safeguarded, and should be directed to consult with their own tax advisors regarding
any IRS reporting requirements that might flow from participation. Note that reimbursement of a participant’s out-of-pocket expenses based on receipts and the provision of tangible gifts (for example, a pill box) are not generally considered taxable income, and Investigators may want to consider the potential tax implications from planned compensation when preparing the protocol; however, participants should confer with their own advisors to determine the scope of any tax liability from participation in the research and Investigators should not attempt to provide tax advice or counseling to potential or enrolled participants.

4.3 Informed Consent Guidelines

The regulations at 45 CFR § 46.116 stipulate that legally effective informed consent of the research participant or the participant’s LAR must be obtained prior to involving the research participant in ‘human subjects’ research. The regulations provide criteria for the information that must be communicated during the informed consent process, how informed consent should be documented, as well as the circumstances under which informed consent - or elements of informed consent - may be waived, as described in more detail in this policy section.

4.3.1 Timing of Informed Consent in Relation to Research Procedures

The consent process should allow the prospective participant or their LAR sufficient opportunity to consider and discuss whether or not to participate, such that the possibility of coercion or undue influence is minimized. The timing of the consent process in relation to the research procedures is often dependent on the nature of the research. For minimal risk research, it may be appropriate to conduct consent and research procedures on the same day. For research that involves more than minimal risk, prospective participants (or LARs) should be provided with information and encouraged to take time to think about the research (e.g. the risks and benefits, the impact of the procedures or study visits on their daily lives) and to talk with family, close friends, and their primary care physician if appropriate, before consenting to participate in the research.

4.3.2 Research Personnel and Obtaining Informed Consent from Participants (or LARs)

Investigators are responsible for obtaining consent, or designating appropriate individuals on the research team to obtain consent, from prospective participants or their LARs. Only members of the research team who have experience in and knowledge about all elements of the study may obtain consent in order to provide a complete and accurate description of the research, and to answer any questions or concerns of prospective participants. The IRB must approve the proposed process for obtaining informed consent, including who on the research team may engage prospective participants in the informed consent dialogue.

4.3.3 Required Elements of Informed Consent Forms

The process of informed consent almost always involves the use of a written document or form as well as a discussion with the participant (or LAR). HSL requires that informed consent materials (forms, scripts, etc.):
- Ordinarily are written at an 8th grade reading level or under (depending on the research population);
- Are provided in a language understandable to the participant or their LAR;
- Define medical terminology and jargon in lay terms;
- Includes information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information;
- Are written in a context that is easy to follow (e.g. inclusive of subject headings, short and concise sentences, numbering or bullet points, timelines for complex procedures, etc.).
• Do not include any exculpatory language through which the participant or their LAR is made to waive or appears to waive any of their legal rights, or releases or appears to release the Investigator, the sponsor, the institution or its agents from liability for negligence.

For research funded by the NIH and/or approved by the HSL IRB on or after January 21, 2019:
• Includes information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information;
• Consent forms must begin with a concise and focused presentation of the key information that is most likely to assist a prospective participant, or their LAR, in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. Generally, this concise summary should include the following information, however, based upon the facts of an individual protocol, the IRB may require that different (or additional) information be presented at the beginning of an informed consent to satisfy this requirement:
  1. The fact that consent is being sought for research and that participation is voluntary;
  2. The purposes of the research, the expected duration of the prospective subject’s participation, and the procedures to be followed in the research;
  3. The reasonably foreseeable risks or discomforts to the prospective subject;
  4. The benefits to the prospective subject or to others that may reasonably be expected from the research; and
  5. Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.
• Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective participant’s or LARs understanding of the reasons why one might or might not want to participate.

Consent materials must include the following elements, consistent with the requirements at 45CFR§ 46.116 and 21CFR§50.25 (when applicable):
(1) A statement that the study involves research;
   • The purpose of the research;
   • The expected duration of participant involvement in the study;
   • A description of the procedures to be followed;
   • Identification of the procedures which are experimental;
(2) Description of any reasonably foreseeable risks or discomforts to the participant;
(3) Description of any benefits to the participant or to others that may reasonably be expected from the research;
(4) Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;
(5) A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained. For FDA-regulated research, this statement must note the possibility that the FDA might inspect the records;
(6) For research involving more than minimal risk, an explanation as to whether any compensation or any medical treatments are available if injury occurs, and if so, what they consist of, or where further information may be obtained. HSL has provided the following consent form statement for the disclosure of compensation for injury to participants:

We will offer you the care needed to treat any injury that directly results from taking part in this research study. If we cannot provide the care directly, we will arrange for the care to be provided to you at a nearby institution. We (and/or the treating provider, as appropriate) reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We
will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

THE SPONSOR MAY REQUEST TO INCLUDE A STATEMENT ABOUT THE INJURY COVERAGE THE SPONSOR WILL OFFER. WHEN THE SPONSOR REQUESTS TO INCLUDE SUCH A STATEMENT, THE STATEMENT MAY BE ENTERED HERE, AFTER THE INSTITUTION’S COMMITMENT TO PROVIDE CARE FOR THE INJURY. FOR EXAMPLE, “In this study, [Sponsor] will pay for medical treatment for any injury that is not paid for by your health insurer if the injury is a direct result of your taking part in the study.”

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury beyond what is described above, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of the study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

(7) Contact information for:
   • A member of the research team for answers to pertinent questions about the research and to report a research-related injury, and
   • A person independent of the research to whom participants may voice concerns or complaints about the research, obtain answers to questions in the event the research staff could not be reached or if they wished to talk with someone other than the research staff, and to obtain information about their rights as a research participant;

(8) A statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled; and that the participant may discontinue participation at any time without penalty or loss of benefits to which they would otherwise be entitled.

For research funded by the NIH and/or approved on or after January 21, 2019:

(9) One of the following statements, if the research involves collection of identifiable private information or identifiable biospecimens:
   (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
   (ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

The following additional information may be required to be included in consent materials, when applicable and appropriate to the research:
   • A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the subject may become pregnant) which are currently unforeseeable (e.g. when the research involves investigational test articles or drugs or other procedures in which the risks to the participants are not well known) (DHHS and FDA);
   • Anticipated circumstances under which study participation may be terminated by the investigator without the participant’s consent (DHHS);
   • Any costs to the individual that may result from participating in the research (DHHS);
• The consequences of a participant’s decision to withdraw from the research, and procedures for orderly termination when withdrawal from the research is or may be associated with adverse consequences (DHHS);

• A statement that participants will be informed of any significant new findings developed during the course of the research which may relate to their willingness to continue in the study (DHHS);

• The approximate number of participants involved in the study (DHHS);

• If the project includes remuneration for participants, the amount, schedule of payments, and any requirements to obtain the remuneration;

• If the study involves genetic analysis, a statement must be included indicating what material will be collected, how it will be collected, for what specific purpose, any procedures for opting out of this aspect of the research (if applicable), whether the material (biological specimens or data derived from the DNA) will be stored for any period of time beyond the study, whether it may be used for other known or future unknown research purposes, whether the research team may discover any incidental findings and if that information will be reported back to the participant, and whether genetic test results will be placed in participants’ medical records;

• For FDA regulated studies that qualify as “applicable clinical trials” under 42 U.S.C. 282(j)(I)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”;

• Any identified Investigator or Institutional conflict of interest that the IRB determines is necessary to disclose to participants.

• The risk of uncovering unreported abuse, neglect or suicidality and the mandatory reporting requirements of the Investigator and research team.

For research funded by the NIH and/or approved on or after January 21, 2019:

• A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

• A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

• For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

As stated in Section 2.2, HSL will ordinarily not conduct research using Broad Consent under the Revised Common Rule. Should the HSL IRB be required to conduct such review, it will abide by the regulatory criteria of the Revised Common Rule at 45 CFR 46.116(d).

The HSL Informed Consent Form Template, found in the HSL eIRB system (also available by contacting the IRB Office), contains the above required elements.

4.3.4 Documentation of Informed Consent

Signed documentation of informed consent is required in the following manner [45CFR§46.117(b) and 21 CFR§50.27 for FDA-regulated research] unless a waiver of consent/documentation of consent is granted (see waiver criteria in Section 4.4):
(1) A written consent document must contain the required elements of informed consent, as outlined in Section 4.3.3. The consent form may be read to the participant or the participant's LAR, and ample time should be given to the participant/LAR to read it before it is signed and dated; or

(2) A short form written consent document, stating that the elements of informed consent required by 46.116 have been presented orally to the participant/LAR, may be used. However, when this method is used, there must be a witness to the oral presentation. The IRB must approve the written summary of what is to be said to the participant/LAR (the written consent document, if one exists for the study, may serve as the summary). Only the short form itself is to be signed and dated by the participant/LAR. However, the witness must sign and date both the short form and a copy of the summary, and the person actually obtaining consent must sign and date a copy of the summary. A copy of the summary must be given to the participant/LAR, in addition to a copy of the short form.

The IRB requires that the research participant (or LAR) sign and date the current stamped/IRB approved consent form, unless a waiver or alteration of consent is approved. The research participant/LAR should be given a copy of the consent document to keep and the person conducting the consent process should encourage the participant/LAR to maintain this copy in the event they have questions during the research, or after the research has ended.

For research funded by the NIH and/or approved on or after January 21, 2019, unless the requirement for documentation of consent is waived by the IRB, informed consent must be documented by the use of written informed consent form (ICF) approved by the IRB and signed (including in an electronic format) by the subject or the subject’s LAR. A written copy must be given to the person signing the ICF.

The ICF may be either of the following:

1. A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject’s LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject’s legally authorized representative; or

2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR and that the key information required by 45 CFR 46.116(a)(5)(i) (See Section 8.1 #5.a) was presented first to the subject, before other information, if any, was provided. When this method is used:
   a. The oral presentation and the short form written document should be in a language understandable to the subject; and
   b. There must be a witness to the oral presentation; and
   c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
   d. The short form document is signed by the subject;
   e. The witness must sign both the short form and a copy of the summary; and
   f. The person actually obtaining consent must sign a copy of the summary; and
   g. A copy of the signed summary must be given to the subject or representative, in addition to a copy of the short form.

4.3.5 Witness to the Consent Process

A witness is required in the following circumstances:
• If the IRB approves the use of the “short form” (see Section 4.3.4 and 4.4.2); and
• When a participant cannot read and the consent document must be read to him or her.

The witness is required to sign and date the consent form. The witness signature attests that the information in the consent form (and other written documents, as applicable to the research) was accurately explained
to and understood by the participant/LAR, and that the informed consent was given freely. The witness should be independent of the research. Translators for non-English speaking participants/LARs (see 4.4.2) may be used as witnesses however Investigators must determine whether the translator is appropriately trained to assess the attestation standard, and if not, a translator and a witness must be retained.

4.4 Guidelines for Waivers or Alterations of Consent Requirements

Under 45 CFR § 46.116, the 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 requirement to obtain consent, provided it finds and documents that:

(1) The research or demonstration project is to be conducted by, or subject to, the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs;

(2) The research could not practically be carried out without the waiver or alteration; and

(3) The research is not FDA-regulated. (For limited circumstances in which informed consent may be waived in FDA regulated research, see Section 13.)

Additionally, the IRB “may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent” or waive the requirement to obtain consent altogether, provided it finds and documents:

(1) The research involves no more than minimal risk to the participants;

(2) The waiver or alteration will not adversely affect the rights and welfare of the participants;

(3) The research could not practically be carried out without the waiver or alteration;

(4) Whenever appropriate, the participants will be provided with additional pertinent information after participation, and;

(5) The research is not FDA-regulated. (For limited circumstances in which informed consent may be waived in FDA regulated research, see Section 13.)

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

(1) That the only record linking the participant and the research would be the consent document, the principal risk would be potential harm resulting from a breach of confidentiality, and the research is not FDA-regulated. In each circumstance, the participant should be asked whether they want documentation linking them with the research, and their wishes will govern; or

(2) That 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.

If the IRB approves waiver of signed consent based on consideration (1), the full consenting process for these participants (including being given a written informed consent document embodying all the elements of informed consent) remains the same except that the participant will have the option to not sign the consent document or have information linking them to the study placed in their medical file.

If the IRB approves waiver of the requirement to obtain a signed written consent form based upon consideration (2), Investigators must fully inform prospective participants about the study, answer their questions and obtain their verbal informed consent. In lieu of a written consent form, the IRB may require the Investigator to provide participants with a written statement about the research. In these circumstances, the Investigator should document the following information in the research files (and any resident/patient medical files, if applicable to the research), and the note to the file should be signed and dated by the person obtaining consent:
• Who was approached;
• A brief summary of what was explained;
• Whether the individual (or LAR) expressed an understanding of the research study;
• That questions (if any) were answered to the participant’s satisfaction;
• That the individual agreed to participate; and
• Whether written information about the study was given to the participant.

For research funded by the NIH and/or approved on or after January 21, 2019, waivers and/or alterations of Informed consent under 45 CFR 46.116(e) and (f) must follow the below guidelines. IRB determinations will be communicated to the Investigator on the IRB approval notice.

In order to approve a request from an Investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an “Alteration”), under this provision the HSL IRB must determine and document that the below criteria are satisfied:

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

In order to approve a request from an Investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an “Alteration”), under this provision the HSL IRB must determine and document that the below criteria are satisfied:

1. Waivers –
   a. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the general requirements of informed consent (Sections 4.3 and 4.3.1), and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

2. Alterations –
   a. An IRB may not approve a request to alter or omit any of the general requirements for informed consent (Section 4.3 and 4.3.1).
   b. If a broad consent procedure is used, an IRB may not alter or omit any of the elements described in 45 CFR 46.116(d).

Waiver or Alteration of Consent in Research Involving Public Benefit and Service Programs

In order to approve a request from an Investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent (an “Alteration”), under this provision the HSL IRB must determine and document that the below criteria are satisfied.

1. 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:
   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; and

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

Restrictions:

1. Waivers –
   a. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements in Sections 4.3 and 4.3.1, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

2. Alterations –
   a. An IRB may not approve a request to alter or omit any of the general requirements for informed consent described in Sections 4.3 and 4.3.1
   b. If a broad consent procedure is used, an IRB may not alter or omit any of the elements described in 45 CFR 46.116(d)

Waiver of documentation of Informed Consent

Under 45 CFR 46.117(c), the Revised Common Rule adds a third condition under which an IRB may waive the requirement for an Investigator to obtain a signed informed consent form. The HSL IRB may approve a request for a waiver of documentation of consent if it finds that:

1. The subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm,
2. The research presents no more than minimal risk of harm to participants, and
3. There is an appropriate alternative mechanism for documenting that informed consent was obtained.

The IRB’s determination regarding waivers will be documented on the IRB approval notice.

4.4.1 Telephone Consent

Obtaining consent over the telephone is not considered documentation of informed consent as required by federal regulations. All reasonable efforts must be made to obtain written informed consent from the participants/LARs. The IRB is aware that some LARs do not live near the resident for whom they are a LAR, and in other circumstances participants and/or LARs may not be physically available to come to HSL for the informed consent process. To accommodate for this fact, Investigators or the research staff responsible for conducting consent may request that the IRB approve a consent process through which they speak with the participant/LAR by phone, and fax or send by mail a copy of the consent document for signature prior to enrollment. Once the consent form is signed and returned to the Investigator, the participant at that point can be considered to be enrolled in the research.

When obtaining informed consent/assent via phone and mail, the following procedures should ordinarily be followed:

1. Two copies of the informed consent form should be mailed to the participant/LAR with instructions to call the PI/research staff when consents are received.
2. When the participant/LAR calls the appropriate research staff to provide consent, the research staff must review the study and consent document with the participant/LAR, asking questions to gauge comprehension, and answer any participant/LAR questions and concerns. The research staff should document the informed consent process for each participant/LAR.
3. After all questions are answered and the research staff believes that the participant/LAR understands the purpose, procedures, as well as the risks and benefits of the study, the participant/LAR should be instructed to sign and date both copies of the consent form, and mail back one signed copy to the research staff and maintain one signed copy for their own records.

4. Once received, the research staff that explained the study should sign the appropriate signature line with current date (not the date they spoke with participant/LAR), and ensure that the participant/LAR signature and date is accurately documented.

It is recommend that the research staff document in a note on the Consent Form, under the PI signature line, that consent was obtained over the phone on the actual date and mailed back (e.g. “Discussed with [person] via telephone on [insert date], and received signed consent form on [insert date].”).

4.4.2 Informed Consent of Non-English Speakers, or with Limited Understanding of English

The federal regulations stipulate that consent materials must be provided to prospective subjects/LARs in a language that is understandable to them. For Investigators who enroll non-English speakers (or those with a limited ability to understand or read materials in English), materials to be used with or by these participants must be translated into a language that is understandable to them. Written consent documents, regardless of the language in which they are written, must contain all of the elements of consent, as noted in Section 4.3.3.

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

(1) The verbal presentation and the short form written document should be in a language understandable to the potential participants/LARs;

(2) The witness should be fluent in both English and the language of the participant/LAR. As noted in Section 4.3.5, Investigators must determine whether the translator is appropriately trained to also serve as a witness to the consent process and if not, a translator and a witness must be retained;

(3) The approved English language informed consent document may serve as the summary, as long as it is read by the witness in the language understandable to the participant/LAR;

(4) At the time of consent,
   a. the short form document should be signed by the participant/LAR;
   b. the summary should be signed by the person obtaining consent as authorized under the protocol;
   c. the short form document and the summary should be signed by the witness.

A copy of non-English language materials to be used with or by participants/LARs should be submitted to the IRB, with an accompanying Translation Attestation Form. The Translation Attestation Form is intended to (1) provide an alternate to back-translations of translated documents, (2) to confirm that each appropriate document has been translated, and (3) to verify the documents’ authenticity to the English version of the IRB approved materials (e.g. consent, data collection forms).

4.5 Posting of Clinical Trial Consent Forms

For research funded by the NIH and/or approved on or after January 21, 2019, the Revised Common Rule includes a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency after the
A clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. This requirement may be satisfied by either the awardee or the Federal department or agency. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website (e.g., confidential commercial information), the department or agency may permit or require redactions to the information posted. Federal guidance or instructions regarding the implementation of this requirement was not available at the time this SOP went into effect. Until federal guidance or instructions are available, when HSL is the prime awardee, Investigators who are the recipient of the prime funding award supporting the research should consult with their sponsor’s grant officer regarding how to satisfy this requirement.

Acceptable public federal websites for posting clinical trial consent forms include:

- Clinicaltrials.gov (preferred); and
- Docket folder on regulations.gov (Docket ID: HHS-OPHS-2018-0021)

### 4.6 Assessing Capacity to Consent to Research

The HSL research subject population includes adults who have limited decision making capacity due to illness, disability, or disease. Both HHS and FDA regulations require that informed consent be obtained for participation in research from the subject or, where the subject lacks capacity to consent, from their LAR.

The capacity of individuals to consent to medical procedures is assessed by a licensed independent practitioner. At HSL, this assessment is conducted routinely for all residents by a medical doctor or nurse practitioner in the Department of Medicine. A minimal data set (MDS) is contained in each resident’s medical record, and includes the results of a mental status exam. For nursing home residents, the MDS is conducted on a quarterly basis. Depending on the nature of the research, and notwithstanding the MDS, the IRB may require additional evaluations as necessary.

If a health care proxy has been activated, it has been determined that the resident does not have the cognitive capacity required to make medical decisions. An activated health care proxy becomes the resident’s LAR, and may consent to the resident’s participation in the procedures involved in the research (see Section 4.6). However, the absence of an activated Health Care Proxy in the medical record should not be interpreted by Investigators as proof the resident has decision-making capacity for a particular research study.

If a potential participant with decisional impairment is capable of exercising some judgment concerning the nature of the research and his or her participation in it, then the Investigator should obtain the participant’s assent in addition to the consent of his/her LAR. A potential participant’s objection to the research, in whatever form, must be respected. Furthermore, once consented, even if by an LAR, if the participant at any time objects to continuing in the research, that objection must be respected and his or her participation will be withdrawn. In this circumstance, the LAR does not need to additionally withdraw the participant’s consent.

When the condition causing a participant’s decisional impairment is of an intermittent or temporary nature, the informed consent process, reliant on consent from the participant’s LAR, should include a mechanism for obtaining the participant’s subsequent and direct informed consent to participate in the research once capacity has resumed. If the participant, upon regaining decisional capacity, declines to continue in the research, his or her decision must be respected and his or her participation will be withdrawn. Health care proxies are activated during the time of impaired cognition, and deactivated when the resident regains the ability to make their own decisions. Research protocols should include plans for addressing this issue with the proxies.
4.7 Legally Authorized Representatives

If a potential participant cannot provide consent, then a surrogate decision maker, or LAR, must consent to the individual’s participation in the research.

The federal regulations at 45 CFR 46.102(i) define “legally authorized representative” as “an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research”. It further states that if there is no applicable law addressing this issue, “legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject’s participation in the procedure(s) involved in the research.” Under Massachusetts law, this means the consent must come either from the legal guardian of the participant, or from the participant’s health care agent (either as appointed under the Massachusetts health care proxy law, or as identified by a health care provider under the common law for obtaining consent to the provision of medical care and associated procedures).

HSL will allow consent to be obtained from the following persons:
• A court-appointed guardian who has clear authority to make health care decisions;
• A person designated as a health care agent under a valid health care proxy, with express authority to make health care decisions;
• A durable power of attorney with express authority to make health care decisions;
• A family member: including a competent spouse, adult child, or competent parent.

HSL residents who have not identified a health care proxy before they lose the cognitive capacity to do so are appointed a guardian by the probate court. The appointment of a guardian is ordinarily requested by HSL or a resident’s family member.
5. **Initial Review of Research**

Investigators must use the eIRB system to submit projects for IRB review and approval. IRB staff will conduct a preliminary review and will inform the PI of any missing materials, and will also recommend edits to materials based on regulatory criteria, and/or HSL IRB preferences.

IRB staff will communicate determinations and approval decisions in writing to Investigators ordinarily within 5 business days of review, and a copy of the notice and any approved materials (such as informed consent forms) will be retained in the eIRB system. IRB staff will copy HSL Administration and Sponsors on review notices as appropriate, or if so requested by the Administration, PI, or Sponsor.

Definitions for terms used in this section may be found in policy Addendum 1 - titled ‘Definitions’.

5.1 **Materials Required for IRB Review**

The following materials must be submitted to the IRB for review, if applicable to the research:

- CV/Biosketch of the PI, key personnel and research staff
- Current human subjects protection training certificates;
- All applicable HSL IRB applications and forms (including eIRB forms and attachments);
- Study recruitment materials;
- Informed consent materials;
- HIPAA Authorization (if not embedded in the Informed Consent Form);
- Data collection forms and study instruments (questionnaires, interview scripts, etc.);
- Study information materials, such as websites or newsletters;
- IRB approval notices from other institutions;
- Agreements related to the Research (e.g. Material Transfer Agreement; Data Use Agreement; Clinical Trial Agreement or other Sponsored Research Agreement);
- Protocol (Sponsor or Investigator if Investigator-initiated);
- Drug and Device brochures;
- Investigator Brochure;
- Data safety monitoring plan and/or charter, if separate from Protocol;
- Materials for reference, such as relevant publications;

5.2 **Determinations of Research, Research involving Human Subjects, Quality Improvement, and Engagement in Research**

Determinations of whether a project meets the definition of Research, Research involving Human Subjects, Quality Improvement, Engagement in Research, and whether the activities meet exemption or expedited review criteria, may be made by the IRB Chair. The IRB Chair has authorized and designated certain IRB members, including the IRB Director, who may also make these determinations. Investigators who wish to obtain a formal determination letter must submit for review through the eIRB system. IRB staff will conduct a preliminary review and will inform the PI of any missing materials, and will also recommend edits to materials based on regulatory criteria, or HSL IRB preferences. IRB staff will communicate determinations in writing to Investigators ordinarily within 5 business days of review, and a copy of the determination will be retained in the eIRB system.
5.2.1 Research and Research Involving Human Subjects

Not all projects conducted at HSL meet the federal definitions of ‘research’, or research involving ‘human subjects’. Only those projects meeting both the definition of ‘research’ and ‘human subjects’ (also referred to as ‘human subjects research’) as defined in this policy require review and approval by the IRB.

5.2.2 Quality Improvement Activities vs. Research Activities

HSL employees and faculty engage in activities to improve the quality of clinical care and service programs for the seniors and their family members who are served by HSL each day. In general, if activities are limited to implementing a practice solely for the purpose of improving patient care or delivering healthcare, or measuring and reporting provider data for clinical, practical or administrative purposes, those activities do not meet the definition of ‘research’. If Quality Improvement (QI) projects involve systematic investigations designed or intended to develop generalizable knowledge (e.g. to evaluate the effectiveness of the proposed program in order to guide policy or clinical practice changes), then the QI project would be considered research.

QI projects may constitute research because the program being implemented qualifies as a research intervention performed to evaluate an untested QI program’s effectiveness (i.e., the program is implemented for a research purpose or is altered or controlled in some way to answer a research question); alternatively, QI projects may contain a research aspect separate and apart from the implementation of the QI program itself if HSL faculty and staff wish to study the implementation of the program (to understand various factors related to how such programs are implemented) beyond the collection of patient or provider data regarding the implementation for clinical, practical or administrative purposes. In the latter case, if the study of the QI program involves “human subjects” it (the study of the QI program) will require IRB review and oversight, even if the implementation of the program itself does not require IRB review and oversight. QI projects that are determined to be research with human subjects require IRB review and approval prior to implementation. See the HSL IRB guidance “Determining Quality Improvement vs. Research Activity” and the checklist that accompanies that guidance, available on the Marcus Institute website.

5.2.3 Engagement in Human Subjects Research

HSL and HSL employees are engaged in a particular human subjects research activity when its “employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.”. Additionally, HSL is considered ‘engaged’ in the research if the Institution receives a direct award from DHHS for the research, regardless of whether the activities will take place at HSL or another institution. The engagement of HSL in non-exempt human subjects research requires HSL IRB review and oversight of the research, or the reliance of HSL on an external IRB (see Section 5.6).

5.3 Exemption Criteria

The HSL IRB follows the criteria at 45 CFR § 46.104 and 21 CFR § 56.104 pertaining to exemptions.

For research funded by the NIH and/or approved by the HSL IRB on or after January 21, 2019:

Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories in paragraph (d) of this section are exempt from the requirements of the federal policy at 45 CFR 46, except that such activities must comply with the requirements of this section and as specified in each category.
Except as described in the previous paragraph, the following categories of human subjects research are exempt from the federal policy at 45 CFR 46:

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students’ opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
   (i) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   (ii) Any disclosure of the human subjects’ responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, educational advancement, or reputation; or
   (iii) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §ll.111(a)(7).

   The IRB may approve the research when it determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
   (A) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   (B) Any disclosure of the human subjects’ responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, educational advancement, or reputation; or
   (C) The information obtained is recorded by the Investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §ll.111(a)(7).

   The IRB may approve the research when it determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the Investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.
(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator’s use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

(5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

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

(ii) [Reserved]

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

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the 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.
Please note that there are two more Exemption Categories (7 and 8) that are part of the regulations, but because HSL does not offer broad consent as an option at this time, these exemptions are not available to HSL Investigators and are therefore not detailed in this policy.

5.4 Research Meeting Expedited Review Criteria

Expedited reviews are ordinarily conducted by the IRB Chair; however the Chair has designated certain experienced IRB members to additionally conduct such reviews. Expedited reviewers have the same authority as the convened IRB, except that research may not be disapproved by expedited procedures. The eIRB system maintains a list of all research reviewed and approved by expedited procedures and that list is available to the convened IRB along with the other materials for review in the eIRB system for each convened IRB meeting.

The Federal Register at 63 FR 60364-60367 published the following applicable categories of research that may be approved by Expedited Review:

Applicability

A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

B. The categories in this list apply regardless of the age of subjects, except as noted.

C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

D. The expedited review procedure may not be used for classified research involving human subjects.

E. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the IRB.

F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review, if continuing review is required and documented by the IRB.

Research Categories

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, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
   b. from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means.

   Examples: (a) hair and nail clippings in a non-disfiguring 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) uncanulated 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 subject or an invasion of the subjects privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electoretinography, 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 non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects.)

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

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

In compliance with 45 CFR 46.110(b)(1) and 21 CFR 56.110, the HSL IRB uses the expedited review procedure to review the following:

(i) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(ii) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

The HSL IRB considers a proposed change to be ‘minor’ if it:
- Does not significantly alter the risk:benefit assessment of the protocol;
- Does not significantly affect the safety of research participants, such as adding significant medical, social or psychological risks;
- Does not involve the addition of procedures, interactions or interventions that are not otherwise eligible for expedited review;
- Does not involve the addition of a vulnerable population not otherwise eligible for expedited review; and
- Does not significantly alter the scientific question or quality of the study.

For research funded by the NIH and/or approved by the HSL IRB on or after January 21, 2019:

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

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

5.5 Research Reviewed by the Convened IRB

Research involving human subjects that does not meet Exemption or Expedited review criteria is reviewed by the convened IRB. Protocols are ordinarily placed on the convened meeting agenda after the IRB staff have pre-reviewed the research materials and determined that there is sufficient information to satisfy approval criteria. If the IRB staff concludes that an application is not sufficient in a material way, the IRB staff will communicate its concerns with the investigator so that revisions can be made before the project is submitted for consideration by the convened IRB.
5.6 IRB Reliance

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

NIH Requirements for Single IRB Review of multisite research applies to all studies that are:
- Funded through grants, cooperative agreements, contracts, or the NIH Intramural Research Program, and
- Involve non-exempt human subjects research, and
- Involve multiple sites, all of which are conducting the same protocol.

NIH Requirements for Single IRB Review of multisite research does not apply to studies that are:
- Funded to foreign awardees and/or conducted at foreign sites, or
- Funded through career development, research training or fellowship awards, or
- Where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy, or
- Collaborative projects in which multiple sites are involved but different sites may complete different parts of the study.

Reviewing and relying IRBs are required to enter into a reliance agreement, or an IRB Authorization Agreement. HSL is a participating institution in SMART IRB, a national reliance agreement and reliance request system. Documentation of reliance arrangements must be kept on file by both the reviewing and relying IRBs. Requests to review or rely should additionally be made by the HSL investigator in the HSL eIRB system.

5.6.1 Relying on an External IRB

The HSL IRB ordinarily relies on the review and approval of an external IRB in the following circumstances:
- The external IRB has been designated as the Reviewing IRB by the Sponsor
- The involvement of the HSL Investigator is limited to data or specimen analysis, or other minimal risk activities that nonetheless are determined to engage HSL in the research;
- The other institution’s reviewing IRB is more properly constituted to review a certain scope or topic of work, or may have better knowledge of the prevailing community attitudes where the majority of the research procedures will take place;
- Other circumstances where the HSL IRB determines that the protection of human subjects will be enhanced, and not in any way undermined, by ceding review authority.

IRBs reviewing research on behalf of HSL should be required to report to the HSL IRB any events related to the research that requires reporting by HSL to OHRP or other federal or state agencies (unanticipated problems involving risks to participants or others, suspensions or terminations of IRB approval, serious or continuing non-compliance, and findings of research misconduct on the part of the Investigator).

Decisions to cede review are ordinarily made by the IRB Director, with IO, Legal/Compliance, and IRB Chair consultation as necessary. The HSL IRB office will make all appropriate arrangements (e.g. IRB Authorization Agreement or use of SMART IRB) with the Reviewing IRB, and will provide a letter to the HSL investigator confirming ceded review/HSL reliance on the external IRB.
For non-exempt research funded by the NIH on or after January 21, 2019, or exempt research for which limited IRB review is conducted, that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution’s reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of 45 CFR 46 (e.g., in an IRB Authorization Agreement, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol).

5.6.2 Accepting Review on behalf of another Institution or non-HSL Investigator

The HSL IRB will ordinarily accept review responsibilities as the IRB of record for another institution or non-HSL investigator on a case-by-case basis, including but not limited to the following circumstances:
- The HSL IRB has been designated as the Reviewing IRB by the Sponsor
- When the primary activities involving research participants take place at an HSL facility under the jurisdiction of an HSL Investigator and the secondary institution’s involvement is primarily financial or limited to minimal risk activities;
- When the study involves personnel from a secondary institution that does not have an IRB but is initiated by an Investigator from HSL who is the Lead Investigator in a multisite study.

Decisions to serve as the reviewing IRB for another Institution are ordinarily made by the IRB Director, in consultation with the IO, Legal/Compliance, and IRB Chair as necessary.

When HSL accepts responsibilities as the IRB of record for another Institution or non-HSL Investigator, the HSL IRB policies and procedures apply to the research.

5.7 Data and Specimen Repositories

A Data or Specimen Repository is a collection of health information derived from patient medical records, research records, other hospital records, biological specimens or data collected through interactions or interventions with patients. Repositories may be used for various purposes, including research, quality improvement and clinical care. The creation and maintenance of a Research Repository are considered “research” activities, to which both DHHS and the HIPAA privacy regulations apply, even before any specific research projects are carried out using the stored materials. IRB review and approval is required prior to the creation of any Research Repository, unless the IRB determines that it does not qualify as “human subjects research” (see Section 5.2), or that it does qualify as human subjects research but meets the criteria for exemption (see Section 5.3). Investigators who wish to create or use Repositories where the primary purpose is to compile data or specimens that may be used or shared for research purposes must submit a Research Repository Application through the eIRB system and should review the HSL IRB Guidance on Creating Research Repositories located on the Marcus Institute website.

5.8 ClinicalTrials.gov

ClinicalTrials.gov is a registry of clinical trials operated by the National Library of Medicine that captures key summary protocol information before and during the trial, as well as summary results and adverse event information of a completed trial. Clinical trial registration is required by the FDA, the NIH, and the International Committee of Medical Journal Editors (ICMJE).
**FDA Requirements:**

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

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

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

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

For more information regarding Applicable Clinical Trials and Responsible Parties, see Elaboration of Definitions of Responsible Party and Applicable Clinical Trials.

**NIH Requirements:**

The NIH policy requires registration of all clinical trials funded in whole, or in part, by the NIH, in clinicaltrials.gov.

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

Timeline for Registration, Updates and Results Reporting in ClinicalTrials.gov:
- Registration must occur within 21 days of enrollment of 1st subject;
- Updates must be submitted at least every 12 months (30 days for Recruitment Status and Primary Completion Date);
- Reporting of summary results must be submitted no later than one year after the completion date. Primary completion date is the date that the final participant was examined or received an intervention for the purpose of collecting the data for the primary outcome measure.
Responsible Party:
The institution that received the funding award is generally considered to be the ‘sponsor’ and responsible for compliance with NIH policies, including clinicaltrials.gov registration, updates and results reporting. At HSL, the Principal Investigator listed on the funding application and responsible for overseeing the trial will ordinarily be the responsible party for registering their trial and meeting clinicaltrials.gov submission requirements.

ICJME Requirements

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

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

Timeline for Registration, Updates and Results Reporting:
- Registration should occur before the first person consents to participate in the research;
- Authors should include a statement that indicates when the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The ICMJE does not require registration of observational studies or studies involving secondary data analyses of primary (parent) clinical trials, but ICJME notes that these types of studies should reference the registration number of the primary trial(s). The ICJME further recommends that, when in doubt of whether registering is required, that Investigators err on the side of registering their trial.
6. Continuing Review of Research

Per 45 CFR 46.109(e) and 21 CFR 56.108(a) and 56.109(f), an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year, except as described in 45 CFR 46.109(f)(1), identified below:

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research is eligible for expedited review in accordance with 45 CFR 46.110;
(ii) Research reviewed by the IRB in accordance with the limited IRB review described in 45 CFR 46.104(d)(2)(iii) and (d)(3)(i)(c);
(iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
   (A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
   (B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Although the revised common rule no longer requires continuing review in the above circumstances, the HSL IRB will require a yearly check-in for the above categories of research.

Continuing review affords the IRB and the Investigator the opportunity to reassess the research and assure that, among other things, risks to research participants are being minimized and are still reasonable in relation to anticipated benefits, if any, to the participants and the knowledge that is expected to result. Continuing review is required while the research is ongoing, and 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.

During continuing review, the HSL IRB pays particular attention to the following:
- Risk assessment and monitoring, including adverse events or unanticipated problems involving risks to participants or others;
- Participant withdrawals and the stated reason for withdrawal;
- Participant or other third party complaints;
- Adequacy of the process for obtaining informed consent;
- Investigator issues (e.g. compliance factors)
- Changes in institutional policies
- Research progress

The eIRB system notifies Investigators by email of upcoming continuing review submission deadlines 45 days prior to the study expiration date. IRB staff will conduct a preliminary review of the submitted materials and will inform the Investigator of any missing materials, and will also recommend edits to materials based on regulatory criteria, and/or HSL IRB policies and preferences.

Investigators who submit continuing review materials after the deadline marked on the continuing review notice run the risk of the protocol expiring before re-approval can be secured. When a protocol approval expires, all research activities must stop (see Section 6.5). IRB staff will communicate in writing to Investigators within 5 days following review whether continuing approval has been granted and any conditions associated with the approval, and a copy of the IRB notice and any approved materials (such as informed consent forms) will be retained in the eIRB record. IRB staff will copy HSL Administration and Sponsors on review notices as appropriate, if so requested.
6.1 **Materials Required for Continuing Review**

Investigators are responsible for providing sufficient materials and information to meet regulatory requirements in time for the IRB to reapprove the study before the expiration date. To receive continuing review, Investigators must submit the following documentation via the eIRB system (all of which will be available to the primary reviewer and the IRB members, where full board review is utilized), as applicable to the research:

- HSL eIRB Continuing Review Application
- Current Personnel Roster;
- Current Protocol Form;
- Current Drug and/or Device Forms;
- Amendment Approval Log;
- Adverse Event/Unanticipated Problems Log;
- Study materials to be used in the upcoming approval period, including:
  - Recruitment materials
  - Consent form(s), short forms, or informed consent scripts
  - Data collection materials (surveys, interviews, etc.)
- Data Safety Monitoring Board (DSMB) report;
- Multi-Center Trial Report;
- FDA (IND/IDE) Annual Report;
- Current IRB approvals from any other reviewing IRB;
- Current Sponsor Protocol, including DHHS-approved protocol, if applicable
- Current product information (e.g. Package Insert, Investigator Brochure, Device Manual, etc.) for each marketed product
- Requests for any modifications to the research (see Section 7);

6.2 **Continuing Review by the Convened IRB**

Continuing review at a convened meeting is required for all studies that have been previously reviewed by the convened IRB, unless the research subsequently qualifies for expedited review (see Section 6). The IRB applies the same approval criteria for, and may take the same IRB actions with respect to, the continuing review of research projects as it does in the initial review, as outlined in Section 2.

6.3 **Yearly Check-in for Research that does not Require Continuing Review**

Research under 45 CFR 46.109(f) that no longer meets the threshold required for continuing review will undergo a yearly check-in process. Investigators will receive notification from the eIRB system 30 days before the anniversary date of IRB approval.

Yearly check-in will require the following information/documentation from the Investigator, as applicable:

- Brief progress report, including plans for the coming year
- Number of participants currently enrolled
- Number of participants enrolled since the previous reporting period
- Verification of any unanticipated problems
- Verification of any changes to the research/research materials and that no changes were made without prior IRB approval
- Verification of any problems with the conduct of the research
• Verification of compliance reporting with the research or Investigators working on the research (e.g. COI, research misconduct, serious/continuing non-compliance, etc.)
• Verification of any complaints from research participants or others
• Status of funding
• Estimated completion date

Materials submitted for the annual check-in will be reviewed by the IRB Director. If the IRB Director believes further review is warranted by the IRB Chair or the full board, the Director will forward the check-in materials as applicable. Materials submitted in the eIRB system are maintained in the eIRB system.

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

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

6.5 Lapse in Continuing Review Approval

Any lapse in IRB approval is handled under the Non-Compliance section of this policy document (see Section 9). Investigators whose IRB approval lapses due to late submission of Continuing Review applications or other required materials must additionally submit an Incident Form via the eIRB system. Investigators should be aware of the following:

• Investigators whose projects have expired must stop all research activities (including recruitment, enrollment, analysis, etc.), and may not resume until the protocol has been re-approved and re-activated, as documented with an IRB approval notice.
• The IRB, its Chair or designee, may allow current participants to continue in some or all research procedures during a period of lapse when it finds an overriding safety concern or the ethical issues involved are such that it is in the best interest of participants (individually or as a group) to continue current activities. Investigators may not continue research on enrolled subjects without the express approval of the IRB based on such a finding.
• Lapsed approval of studies requiring convened IRB review undergo the same procedures outlined in Section 5.5 of this policy document.
• Investigators whose approval lapses due to IRB administrative error (i.e. materials were received by the IRB office in a timely manner, but the office did not review in a timely manner) are not required to file an Incident Form, although all study activities must cease until re-approval is confirmed with an IRB re-approval/re-activation notice.
• If a Continuing Review Application is not submitted within one month after expiration, the study will ordinarily be closed by the IRB office and the Investigator notified in writing, with a copy to the Investigator’s HSL Department Head and the Grants Office, if study funding is awarded to HSL. The Grants Office will notify funding agencies or sponsors of lapses in approval, as appropriate with the criteria/stipulations of the sponsor; no funds will be distributed for an unapproved study involving human subjects (see Section 2.14.2). Once a study has been closed, a new eIRB application must be submitted and approved before an Investigator may continue with the research.
• A single lapse in continuing approval does not require reporting to institutional officials, OHRP or other regulatory agencies. However, multiple lapses in approval may constitute serious or continuing non-compliance with IRB, DHHS or FDA requirements and, if so found, will require notification to institutional officials, OHRP and other regulatory agencies, as applicable. The serious and continuing nature of non-compliance is determined by the IRB, and outlined in Section 9 of this policy document.

6.6 Determining the Continuing Review Date

Continuing approval of research will maintain a fixed annual date of approval, as long as the research is re-approved within 30 days prior to the expiration date. If conditional approval is granted at initial review, the effective date of approval (and the first date by which continuing review must occur) will be the date that the Chair and/or Primary Reviewers determine that the conditions of approval have been satisfied (see Section 2.15.2), unless otherwise specified by the IRB. When conditional approval is granted on continuing review, the effective date of approval will be the same fixed annual date, as long as the conditional approval is granted within 30 days prior to the expiration date (whether or not the conditions are met by that date).

6.7 Study Closure

In addition to the failure to submit a Continuing Review Application within one month following expiration (see Section 6.5), a research project may be closed when it no longer involves human subjects. A research project no longer involves human subjects once the Investigators have finished obtaining data through interaction or intervention with subjects or obtaining identifiable data about, or biospecimens from, the subjects.

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

To close a study, Investigators must submit a closure request through the eIRB system.
7. Modifications to Approved Research

Federal regulations at 45 CFR § 46.108(a)(3)(ii & iii) and 21 CFR § 56.108(a)(4) require IRBs to review proposed changes in research activity and to ensure that such changes are not initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to research participants.

IRB staff will conduct a preliminary review of submitted materials for the modification (see Section 7.1) and will inform the Investigator of any missing materials, and will also recommend edits to materials based on regulatory criteria, HSL IRB policies and procedures, and/or HSL IRB preferences.

IRB staff will communicate in writing to Investigators ordinarily within 5 days of review, and a copy of the IRB notice and any approved materials (such as informed consent forms) will be retained in the eIRB record. IRB staff will copy HSL Administration and Sponsors on review notices as appropriate, or if so requested by the Administration, PI, or Sponsor.

7.1 Materials Required for Modifications

Changes to an approved research project (including new materials or modifications to existing materials) must be submitted via the eIRB system. Any changes to the study must be reflected in all applicable study materials (e.g. protocol, consent form, etc.). Revised materials must be submitted with a tracked-changes version and a clean version, and the clean version should list the new version date and/or number. Changes to study personnel may be made on the Personnel Roster. If a modification is the result of new findings that may affect participants’ willingness to continue in the study, those new findings must be communicated to study participants and Investigators should submit a description of the plan to apprise enrolled study participants of this new information, which must be approved by the IRB before it is implemented.

The following documents must be submitted via the eIRB system by the Investigator (or designated study personnel), as applicable, and will be available to all IRB members for convened or expedited review:

- eIRB modification Request and the required materials indicated throughout the eIRB application;
- Personnel Roster (if it is a separate document from the eIRB system) and the required materials indicated on the form;
- Clean copies of amended materials, and tracked changes version of those materials;
- Supporting documentation for the amendment (e.g. DSMB/adverse/unanticipated event reports, amended Sponsor Protocol, newly developed materials, etc.);
- IRB approval of the amendment from other institutions reviewing the research;
- New or modified grant/funding applications/contracts;
- Citations of current findings that might affect the risk:benefit balance of the study;
- Other materials, as applicable or if so requested by the IRB.

7.2 Modification Review

Modifications to research that propose more than minor study changes must be reviewed at a convened IRB meeting. ‘Minor changes’ are changes that do not affect the safety of participants, or alter in any way the scientific integrity of the study, or include a procedure for which expedited review is not permissible. Criteria for approval of amendments by the convened IRB are the same criteria outlined in Section 5.5 of this policy document.

Changes that are determined to be ‘minor’ by the IRB Chair or her designee, and meet expedited review criteria, may be reviewed by expedited procedures as outlined in Section 5.4 of this policy document.
7.3 Modifications to Research to Eliminate an Immediate Hazard to Participants

If an Investigator has changed a study procedure or process to eliminate an immediate hazard to participants, an initial report to the IRB office should occur via telephone or email as soon as possible but no later than within 5 business days of the event. Investigators are required to submit an Incident Report via the eIRB system within one week of the event, unless otherwise specified by the IRB office. Such modifications will be reviewed as a protocol deviation under the Protocol Deviation and Issues of Non-Compliance policies outlined in Section 9.

The Incident Report will be reviewed by the IRB Chair, who will determine whether the modification to the research ensures the participants’ continued welfare. The incident will be reported at the next convened IRB meeting, unless an emergency meeting is required to review the incident. Depending on the facts and circumstances, the Investigator may be required to suspend the research (or a portion of the research) until any necessary information or modifications have been reviewed and approved. Any suspensions to the research project will be reviewed under the policies outlined in Section 10.
8. **Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others**

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

8.1 **Definitions (all definitions are those of DHHS, unless otherwise specified)**

*Adverse event:* Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and psychological harms. (In FDA regulated studies, the term “adverse event” is generally understood to mean any untoward medical occurrence associated with the use of an FDA regulated product. More specific drug and device definitions are addressed below.)

*External adverse event:* From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by Investigators at other institutions engaged in the clinical trial (e.g. Non-HSL research sites, sites not under HSL IRB review, sites with a non-HSL PI).

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

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

*Serious adverse event:* Any adverse event temporally associated with the subject’s participation in research that meets any of the following criteria:
- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity (under the FDA drug regulations this includes “or the substantial disruption of the ability to conduct normal life functions”);
- results in a congenital anomaly/birth defect;
- or any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Unanticipated problem involving risks to subjects or others:* Any incident, experience, or outcome that meets all of the following criteria:
1. unexpected (in terms of nature, severity, or frequency) given
(a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
(b) the characteristics of the subject population being studied;
2. related or possibly related to a subject’s participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

**Unexpected adverse event:** Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:
1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in
   (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable Investigator brochure, and the current IRB-approved informed consent document, and
   (b) other relevant sources of information, such as product labeling and package inserts; or
2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

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

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

### 8.2 Reporting Requirements to the IRB

Investigators must report to the IRB any unanticipated problems involving risks to subjects or others (see definitions in 8.1, and figures 1.1 and 1.2). Investigators should make an initial report via telephone or email as soon as possible and within 5 business days of learning of the event. Investigators are required to submit an incident report via the eIRB system, as well as a written report to the study sponsor or FDA (if applicable), within one week of the event unless otherwise specified by the IRB office.

Incidents requiring reporting to the IRB include:
- Information that indicates a change to the risk or potential benefits of the research, such as
  - An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits might be different from those initially presented to the IRB;
  - A paper is published from another study that shows that the risks or potential benefits of the research might be different from those initially presented to the IRB.
- Breach of privacy;
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Incarceration of a participant in a protocol not approved to enroll prisoners;
- Any event that requires prompt reporting to the sponsor pursuant to the research protocol or other sponsor written instruction;
- Sponsor imposed suspension for risk;
- Complaint of a participant when the complaint indicates unexpected risks, or which cannot be resolved by the research team;
- Protocol violation (an accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at risk of increased harm.

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

![Venn diagram](image)

Under 45 CFR part 46: Do not report A, Do report (B+C)

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

![Algorithm](image)

An adverse event occurs in one or more subjects:

1. Is the adverse event unexpected in nature, severity, or frequency?
   - NO
   - YES

2. Is the adverse event related or possibly related to participation in the research?
   - NO
   - YES

3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? **NOTE:** If the adverse event is serious, the answer is always YES.
   - NO
   - YES

Report the adverse event as an unanticipated problem under 45 CFR part 46

The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46

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

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

Data Safety Monitoring Boards (DSMBs) and Committees (DSMC, or SMCs) required for interventional clinical trials and multi-site clinical trials. Consistent with NIH and FDA policy, data safety monitoring should be commensurate with risks. The methods and frequency of monitoring directly correlate to the degree of risk involved for the study participants. A DSMB or DSMC is ordinarily relied upon to determine safety and effectiveness of a trial, and to recommend the closure of a trial when significant risks or benefits have developed, or when a trial is unlikely to be successful.

The HSL IRB may rely upon the DSMB/C review of serious and other adverse events and unanticipated problems that occur at external sites and under the jurisdiction of a reviewing IRB. Only those external events that are determined to be ‘unanticipated problems involving risks to participants or others’ (see figure 1.2) should be reported by the Investigator to the HSL IRB. Internal events, as outlined in Sections 8.1 and 8.2 of this policy document, must be submitted to the HSL IRB.

If a study has a DSMB/C, the Investigator must submit the data safety monitoring report to the IRB office as soon as it is available. DSMB/C reports should include a statement indicating that the data have been reviewed, the date of review and a summary of specific findings of the research study.

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

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

8.4 IRB Review of Reported Events

The IRB Staff will consult with the IRB Chair and work with the Investigator upon notification of a reported event. The following documents are ordinarily provided/available via the eIRB system to the Chair and/or convened IRB to review, as applicable:

- Event report(s) – including any previous events related to the study and any supplemental materials accompanying the report;
- HSL IRB Protocol materials (including relevant initial and continuing review materials, informed consent forms, etc.);
- Sponsor protocol;
- DSMB/C report
• The grant or contract associated with the protocol;
• Any other materials of relevance or if so requested by the IRB.

The Chair, or her designee, will review the report and determine whether the problem (1) is unexpected; (2) related or possibly related to the research, and (3) indicates that participants or others are at increased risk of harm. If all criteria are met, the problem is considered to be an unanticipated problem involving risks to participants or others and requires review by the convened IRB. In the review of the event, the Chair may:
• Require additional information from the Investigator;
• Require additional information from any additional reviewing IRBs;
  Contact other HSL IRB members or experts in the field for consultation as to the degree or level of risk to participants;
• Request review of the event at the next convened meeting (if the risk upon discovery is not considered an immediate risk to other participants);
• Call an emergency meeting, if the problem and risk is such that study procedures need to be suspended (for more information on study suspensions, see Section 10).

When an event is reviewed by the convened IRB, the Board will review the Chair’s determination to confirm that the event is (1) unexpected; (2) related or possibly related to the research, and (3) indicates that participants or others are at increased risk of harm. The Board may initiate an investigation into the facts underlying a reported event as necessary to reach a reasoned determination. The investigation may be conducted by the Board itself, a subcommittee, or with the assistance of external consultants as appropriate. If, after developing the facts appropriately, the Board confirms that the above stated criteria are all met, the event/problem is confirmed to be an unanticipated problem involving risks to participants or others. As a result of this determination, the IRB may require any corrective action it deems appropriate, including but not limited to one or more of the following:
• Decide that no further action is necessary and that the research may continue as designed (whether temporarily suspended or not);
• Require further investigation by an IRB member or a consultant;
• Require modifications to the study/protocol and/or procedures necessary to minimize risks to participants;
• Require that additional information regarding risks be provided to current and/or past participants, and determining when this information should be provided;
• Require notification to current participants when information may relate to their willingness to continue to take part in the research;
• Require modification to the consent process and/or form to accurately reflect the nature, frequency or severity of the event;
• Require re-consenting current participants in the study;
• Require modification of the continuing review schedule;
• Require monitoring of the research procedures and consent process;
• Suspend enrollment of new participants, or suspend some or all of the study procedures and/or data analysis;
• Terminate the study approval;
• Refer the matter to other institutional offices or committees as appropriate.

If the Chair and/or IRB determine that an event does not meet the criteria of an unanticipated problem involving risks to participants or others but there exists concern about the research, the Chair and the IRB have the authority to require implementation of the actions listed in this section and to devise an alternative solution if the circumstances so dictate.
IRB Staff will send the Investigator written notice of any determinations made by the IRB/Chair and the reasons for that action, ordinarily within five working days of review. However,

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

8.5 Reporting Requirements to Authorities

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

The IRB Director will forward any such determinations made by the convened IRB within one week to the following institutional officials, and federal agencies as appropriate:

- The HSL Institutional Official. The IO will contact (or will instruct the IRB Director or General Counsel and Chief Compliance Officer to contact) any additional institutional authorities, such as the HSL President, Chief Executive Officer, Director of the Marcus Institute & Vice President for Academic Medicine, Chief Medical Officer, as appropriate;
- The HSL General Counsel and Chief Compliance Officer;
- The HSL Grant Administrator, who may be instructed to notify the Sponsor;
- Any collaborating HSL department or external institution involved or engaged in the conduct of the research, as appropriate;
- Any additional IRBs and institutions involved in the research (for multi-site studies, subcontracts, IRBs and institutions relying on HSL IRB review);
- OHRP, when the research is DHHS funded;
- The FDA, when the research is FDA-regulated; and
- Any additional federal agencies involved when the research is subject to those agencies.
9. **Protocol Deviations and Issues of Non-compliance**

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

9.1 **Definitions**

**Protocol Deviation** is any departure in the research activity from the current IRB-approved protocol and approved study materials (e.g. recruitment fliers, consent forms, surveys, etc.). Protocol deviations are non-compliance with the IRB-approved protocol or approved study materials.

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

**Minor Non-Compliance** is a noncompliant event that does not impact research participant safety, compromise the integrity of study/data, violate participant rights or welfare or affect the participant’s willingness to continue in the research. Examples of minor non-compliance include:

- Minor wording changes on a survey without prior IRB review and approval;
- Altering the time required for an interview without prior IRB review and approval;
- Minor changes to study participant documents (e.g. correcting a phone number or address) without prior IRB review and approval;
- The failure to conduct a study visit within the time-frame required by the protocol;
- Using a prior version of the approved informed consent form to enroll a subject due to inadvertent clerical error where there is no substantive content difference between the prior and currently approved versions;
- Lapses in continuing IRB approval of research due to missed deadlines (where no research is conducted during the period of lapse);
- Failure to obtain a determination of exemption or non-human subjects research from the IRB before such research is conducted.

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

- Enrolling research participants in violation of inclusion and exclusion criteria but are enrolled in a protocol with possible health-related consequences;
- Failure to obtain prospective IRB approval before conducting or continuing research or implementing a change in research procedures that may impact the balance of risks and benefits to subjects;
- Lack of legally effective informed consent of research participants;
- Failure to report an unanticipated problem involving risks to participants or others, including adverse events that qualify as unanticipated problems involving risks to participants or others.

**Continuing Non-Compliance** is a pattern of non-compliance that indicates an unwillingness to comply with or a lack of knowledge that may lead to an adverse effect on the rights and welfare of participants or may place participants at an increased risk of harm, or jeopardize the integrity of the study data. Examples of continuing non-compliance include:
• Repeated instances of allowing a study (or multiple studies) to expire before it/they is/are re-approved;
• Repeated failure to respond to IRB inquiries or requests for documentation;
• Repeated failure to respond to and resolve any study conditions; or
• Other instances of repeated minor non-compliance, each of which standing alone would not necessarily be serious but are part of a pattern of disregard for applicable requirements and suggest a sub-standard approach to the conduct of research.

9.2 Investigator Reporting Requirements

Investigators are required to report to the IRB any protocol deviations or occurrences of non-compliance or other events that are not consistent with the IRB approved protocol (even if unintended). Investigators should make an initial report via telephone or email as soon as possible but no later than within 5 business days of learning of the event. Investigators are required to submit an Incident Report via the eIRB system within one week of the event, unless otherwise specified by the IRB office.

Investigators should report their own deviations and occurrences of non-compliance. However, there are times when allegations of non-compliance are reported, in written or oral format, by those either within the research team, or outside of the research team, including by participants in the research or their families. Allegations of non-compliance may be submitted directly to the IRB office, to the Institutional Official, or to the General Counsel and Chief Compliance Officer. All allegations (including those that are anonymous) that come to the attention of the Director of the IRB, Institutional Official or General Counsel and Chief Compliance Officer will be investigated promptly.

9.3 IRB Review of Protocol Deviations and Non-Compliance

Upon receipt of an Incident Form, or an allegation or complaint of non-compliance through other means, the IRB Director, either alone or through a sub-committee of the IRB or ad hoc panel assembled for this purpose and appointed by the Director, will review the Report/allegation with the project file, discuss the Report/allegation with the Investigator and any additional parties, as necessary, and will review any other materials and consult with any outside experts as deemed necessary. The IRB has the authority to sequester any records that it feels are necessary to evaluate an allegation. The IRB Director will provide the IRB Chair with a summary of findings, as well as the Incident Form (or summary of the allegation if received in another format) and project file or eIRB submission material for review. The Chair (and/or designee, if appropriate) will review the Incident Form or allegation, and other relevant information contained in the project or eIRB file in order to determine whether the Report/allegation meets the definition of serious or continuing non-compliance.

If the Chair believes that the non-compliance is not serious or continuing, the Chair may determine the following corrective actions, which will be sent to the relevant Investigator and/or member of the research team by IRB staff within 5 business days of the review:
• Require further education in research methods or human subject protections for the Investigator and/or research team;
• Require changes to the protocol, consent form or process, or study procedures or processes to avoid future incidents of non-compliance;
• Refer the event to a convened IRB meeting for further review;
• Refer the event to other organizational entities [e.g., Institutional Official or General Counsel and Chief Compliance Officer for allegations of research misconduct (e.g. fabrication or falsification of data, or plagiarism)].
If the Chair believes that the non-compliance is serious or continuing, the Report/allegation will be referred to the next scheduled convened IRB meeting. The convened IRB will review all available materials (including reports from any sub-committee investigations or external experts asked to review the matter, communications and information provided by the Investigator, study materials, etc.) prior to making a determination of whether the non-compliance is serious or continuing, and depending on its finding will impose any corrective actions it requires of the Investigator and/or members of the research team. The actions that the convened IRB may take include, but are not limited to:

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

At any time during the IRB review process, the Investigator may request a meeting with the IRB staff, Chair, or request time to discuss the issue at a convened IRB meeting.

9.4 Research Participant Protection and Issues of Non-Compliance

At any time during an inquiry or investigation, the IRB may determine that it is necessary to suspend enrollment of new research participants or to suspend approval of a research project to ensure the protection of research participants, to preserve the integrity of the study, or to preserve the integrity of the HSL research program. Ordinarily, the IRB will not suspend approval of research studies until the Investigator has had an opportunity to respond to the allegation(s) of non-compliance; however, such opportunity may occur after the suspension where the IRB believes there is an immediate risk to participants or the integrity of the data. See Section 10 for more information on Suspensions and Terminations of Research.

9.5 Coordination with Other Investigative Processes

As appropriate, the IRB will cooperate with other HSL offices or committees, or with federal agencies such as OHRP or the FDA, which may be conducting an inquiry, investigation, review or audit involving an Investigator or research study about whom or which the IRB has knowledge or documentation. Upon receipt of notification of an investigation by federal agencies, the following HSL authorities must be notified: Institutional Official, General Counsel and Chief Compliance Officer, Vice President for Research Administration, IRB Director, IRB Chair, President and Chief Executive Officer.

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

9.6 Investigator Notification

The IRB staff or Chair will ordinarily notify the Investigator of serious or continuing non-compliance determinations and any required corrective actions within two business days of the convened meeting at which the determination was made, or immediately following the meeting if the determination was to suspend or terminate the research (see Section 10). An official letter from the IRB will be sent to the Investigator within 5 business days (see Section 9.8).

9.7 IRB Non-Compliance with Regulations and Policies

The IRB is responsible for carrying out its responsibilities in compliance with applicable federal regulations, state laws, and its own policies. In the event that the IRB is alleged to be non-compliant with these regulations, laws, or policies, the IRB Director, or any other third party bringing an allegation, will present the allegation(s) of non-compliance to the Research Compliance Committee, which is normally comprised of the HSL General Counsel and Chief Compliance Officer, the Vice President for Research Administration, and the IRB Director. The IRB Director will recuse him/herself from the Research Compliance Committee reviews, discussions and determinations relating to the IRB. The remaining members of the Research Compliance Committee may appoint a third ad hoc member for purposes of reviewing the allegations of IRB non-compliance if they feel that an additional perspective or vote is warranted; such third member may not be an individual who serves on the IRB and should be someone sufficiently familiar with the IRB’s role and responsibilities to evaluate competently the allegations.

The Research Compliance Committee, constituted to review allegations of IRB non-compliance, may perform a preliminary assessment to determine whether the allegation is entirely without merit and would not be further clarified or supported by additional fact-finding, in which case it is empowered to dismiss the allegations without further action. Assuming that it finds that there may be facts under which a finding of non-compliance would be appropriate, the Research Compliance Committee will determine, after sufficient and appropriate fact-finding, whether the allegation has merit and, if it does, whether the non-compliance is serious and/or continuing, based on the criteria listed in Section 9.1, and whether the event requires reporting to the HSL Compliance Committee, the HSL Board (and/or a Board Committee), and/or to external authorities per Section 9.8.

Examples of potential IRB non-compliance include (but are not limited to):

- Administrative errors by the IRB resulting in a lapse of a study approval (e.g. not processing continuing review paperwork that has been submitted by the Investigator in a timely manner, not achieving quorum to re-approve research before the expiration date, etc.);
- Failure to apply appropriate regulations to the review of research with special considerations, for example research on vulnerable populations or investigations of FDA regulated products;
- Failure to document regulatory determinations, or failure to appropriately retain such documentation;
- Failure of IRB members to recuse themselves from the review of research in which they have a conflict of interest; and
- Granting waivers of consent or authorization under circumstances where the required criteria are not met.

Corrective actions that may be assigned to the IRB by the Research Compliance Committee include but are not limited to:

- Imposition of remedial education for IRB staff, Chair, and/or IRB members;
• Ensuring the availability of additional guidance at IRB meetings by relevant experts;
• Review of IRB files, and other IRB documentation (e.g. meeting minutes, review letters, correspondence with Investigators or research staff);
• Suspension of IRB staff, Chair, and/or IRB members;
• Removal of IRB staff, Chair, and/or IRB members;
• Other actions as deemed appropriate by the Research Compliance Committee.

9.8 Reporting Requirements to Authorities

When the IRB makes a determination of serious or continuing non-compliance, the following individuals or entities must be notified in writing within one week:
• The Principal Investigator and Co-Investigators;
• The Investigator’s Department Head (and any additional Department Heads if the Investigator holds multiple professional appointments)
• The Institutional Official, who will notify any additional HSL institutional authorities (e.g. President and CEO, General Counsel and Chief Compliance Officer)
• The Grants Office (where sponsored research funds are supporting the research), which will notify the study sponsor.
• Any additional HSL departments involved in the conduct of the research;
• Any additional IRBs and institutions involved in the research (for multi-site studies, subcontracts, IRBs and institutions relying on HSL review);
• FDA, when the research is FDA-regulated;
• OHRP, when the research is subject to its jurisdiction; and
• Any additional federal or state agencies involved when the research is subject to those agencies.
10. Suspension or Termination of Research

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

10.1 Definitions

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

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

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

10.2 Investigator Reporting Requirements

Investigators are required to report to the IRB when the decision is made to voluntarily suspend or terminate research (e.g. a voluntary hold). Investigators ordinarily make these decisions at the recommendation or direction of a DSMB/C, research sponsor, or contract research organization, or based on their own assessment. Investigators should discuss with the IRB Director the most appropriate reporting mechanism (e.g. incident report, amendment, study closure). Investigator-initiated voluntary holds may require reporting to authorities (see Section 10.5) if the IRB finds that there is serious or continuing non-compliance, or unanticipated problems involving risks to the research participants or others, underlying the voluntary hold.

10.3 IRB Determinations to Suspend or Terminate Research

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

The IRB may impose the corrective actions it deems necessary to ensure that the circumstances and/or non-compliance that formed the basis for the IRB’s suspension or termination of the research are mitigated and prevented in the future. Such corrective actions may include, but are not be limited to, the corrective actions outlined in sections 9.3 and 10.5.

10.4 Investigator Notification

The IRB staff or Chair will ordinarily notify the Investigator of determinations to suspend or terminate the research immediately following the convened meeting at which the determination was made. A letter from the IRB will be sent to the Investigator within 5 business days, outlining the IRB’s determination and any
required corrective action plan. Investigators shall have the opportunity to respond to the suspension or
termination and offer new procedures or a new research plan to protect the rights and welfare of the
participants, which will be considered by the IRB, in conjunction with the Investigator’s implementation
of any required corrective actions, in evaluating whether the research may be allowed to be re-activated (in
the case of suspension) or re-approved (in the case of terminations) at a later date.

10.5 Research Participant Protection, Post Suspension/Termination

Depending upon the nature of the suspension or termination and the potential risk to participants, the IRB
may require any of the following to ensure the seamless care of research participants and the mediation of
any risk presented by the suspension, termination, or the underlying circumstances that led the IRB to
suspend or terminate the research:
• Notifications to the participants;
• Re-consent using a modified informed consent form before continuation in the study may occur;
• Notifications to the participant’s health care provider;
• If participants are enrolled in a clinical study involving a test article (drug or device) or treatment of
any kind, procedures may include:
  o tapering-off of a drug or device
  o a final study visit that may involve laboratory tests or physical exams
  o arrangements for continued care or treatment by the participant’s physician or a referral to an
    appropriate physician or another Investigator
  o Additional participant follow-up and reports to the IRB for a period of time beyond that originally
    contemplated in the protocol
• Temporary or permanent transfer of the responsibility of the research to another Investigator;
• Other procedures or corrective actions as determined by the IRB.

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

10.6 Reporting Requirements to Authorities

When the IRB suspends or terminates the approval of a study (or any portion of the approval) due to serious
or continuing non-compliance or one or more unanticipated problem(s) involving risks to participants or
others, the following individuals or entities must be notified in writing within one week:
• The Investigator and Co-Investigator;
• The Investigator’s Department Head (and any additional Department Heads if the Investigator holds
  multiple professional appointments)
• The Institutional Official, who will notify any additional HSL institutional authorities (e.g. President
  and CEO, General Counsel and Chief Compliance Officer)
• The Grants Office (where grants are supporting the research), which will notify the study sponsor
  pursuant to the terms of the applicable research contract.
• Any additional HSL departments involved in the conduct of the research;
• Any additional IRBs and institutions involved in the research (for multi-site studies, subcontracts, IRBs
  and institutions relying on HSL review) pursuant to the terms of any applicable collaboration
  agreements;
• FDA, when the research is FDA-regulated;
• OHRP, when the research is subject to its jurisdiction; and
• Any additional federal or state agencies involved when the research is subject to those agencies and to the extent reporting is mandated.
11. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule’s Application to Research Activities

11.1 Definitions

**Affiliated Covered Entity** - Legally separate health care providers (or health plans or clearinghouses) that are under common ownership or control and that choose to comply with HIPAA privacy and security laws and regulations as one covered entity. Hebrew SeniorLife, Inc. and its affiliates all operate as a single Affiliated Covered Entity under HIPAA.

**Authorization** - Document designating permission. The HIPAA Privacy Rule requires written authorization or waiver of authorization for the use or disclosure of identifiable health information for research (among other activities).

**Business Associate** - An outside person/entity that performs a service on behalf of a health care provider (including a researcher) or the health care institution during which individually identifiable health information is created, used, or disclosed (e.g., web hosting or data storage companies, third parties that handle billing for a research study, or recruitment and screening, if PHI is created, used or disclosed).

**Data Use Agreement** - A written satisfactory assurance between the covered entity and a limited data set recipient (e.g., a researcher) requiring agreement by the recipient to various terms, including that the data will only be used or disclosed for specific purposes, that the limited data set will be protected, that the recipient will notify the covered entity of any unauthorized uses or disclosures of which it becomes aware, and that the recipient will not identify the information or contact the individuals whose information comprise the limited data set.

**Decedents** - Deceased individuals (Note: Individually identifiable health information pertaining to individuals that have been deceased for more than 50 years is not protected under HIPAA).

**De-identified** - Under the HIPAA Privacy Rule, data are de-identified if either (1) an expert determines that the risk that certain information could be used to identify an individual is "very small" and documents and justifies the determination, or (2) the data do not include any of the following eighteen identifiers (of the individual or his/her relatives, household members, or employers) which could be used alone or in combination with other information to identify the subject: names, geographic subdivisions smaller than a state (including zip code), all elements of dates except year (unless the subject is greater than 89 years old), telephone numbers, FAX numbers, email address, Social Security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers including license plates, device identifiers and serial numbers, URLs, internet protocol addresses, biometric identifiers, full face photos and comparable images, and any unique identifying number, characteristic or code; note that even if these identifiers are removed, the Privacy Rule states that information will be considered identifiable if the covered entity knows that the identity of the person may still be determined.

**Disclosure** - A release of individually identifiable health information to anyone or any entity outside of HSL.

**Health Care Operations** - Institutional activities that are necessary to maintain and monitor the operations of the institution.

**Health Information** – Any information, including genetic information, in any form (oral, written or otherwise) that relates to the past, present or future physical or mental health of an individual. That...
information could be created or received by a health care provider, a health plan, a public health authority, an employer, a life insurer, a school or university or a health care clearinghouse.

**Individually Identifiable Health Information** - A subset of health information that identifies the individual or can reasonably be used to identify the individual.

**Limited Data Set** - A data set that has been stripped of certain direct identifiers and that may be used for research, public health or health care operations without individual authorization or IRB waiver of authorization. A limited data set is defined as PHI that excludes the following direct identifiers of the individual or of relatives, employers or household members of the individual: names; postal address information, (other than town or city, State and zip code); telephone and FAX numbers; electronic mail addresses; SSN; medical record numbers; health plan beneficiary numbers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plates; device identifiers and serial numbers; web universal resource locators (URLs); internet protocol (IP) address; biometric identifiers, including finger and voice prints; full face photos, and comparable images.

**Protected Health Information (or PHI)** - Individually identifiable health information transmitted or maintained in any form. PHI as used in this policy, consists of any information about an individual, including very basic information such as their name or their age, that
(1) relates to the past, present, or future physical or mental health or condition of the individual, the provision of health care to the individual, or the past, present, or future payment for the provision of health care to the individual, and
(2) either identifies the individual, or could reasonably be used to identify the individual. Protected health information may be in any form, including spoken, written, or electronic form. Examples of protected health information include, but are not limited to, medical records, medical data on information systems, and applications for health or disability benefits.

**Waiver of Authorization** - Under limited circumstances, a waiver of the requirement for authorization for use or disclosure of protected health information may be obtained from the IRB by the researcher.

### 11.2 Protected Health Information and Research Data

HIPAA privacy regulations impose specific requirements regarding how certain PHI may be used or disclosed for various purposes, including research. It is the policy of HSL, in accordance with HIPAA, that research participants have the basic rights of confidentiality and privacy with respect to their health information. In general, these rights require that participants give written permission before HSL may use or disclose their health information for research purposes, unless certain exceptions (outlined herein) apply.

Protected health information obtained by HSL may not be used internally or disclosed to any persons or organizations outside of HSL for research purposes unless it is in accordance with this policy and applicable legal requirements. HSL Investigators requesting access to protected health information for research purposes should be directed to submit their request to the IRB.

The IRB will be responsible for ensuring that the terms of this policy regarding access to and use or disclosure of PHI for research purposes are followed. Investigators who believe that their research is exempt from IRB review and oversight pursuant to Section 5.3 must nonetheless receive approval from the IRB (and HSL’s Privacy Officer, as appropriate) before utilizing PHI for research purposes.

As a general rule, the IRB may approve the use or disclosure of PHI for research purposes when:

- The Investigator can demonstrate that the subject has given, or will give, valid authorization (see Section 11.3);
• The Investigator has obtained or will obtain the informed consent of the individual to participate in the research, or a waiver of such informed consent, prior to April 14, 2003 (this exception ceases to apply if informed consent is sought from the individual after April 14, 2003);
• The IRB approves a waiver of the individual authorization requirement (see Section 11.4);
• The PHI to be used or disclosed is a Limited Data Set (see Sections 11.1 and 11.5) and the external recipient institution of the information and HSL sign a Data Use Agreement to protect the privacy of such information;
• The information is completely de-identified in accordance with HIPAA’s standards (in which case the information would not constitute PHI);
• For reviews preparatory to research (with certain required Investigator representations); OR
• For research on the protected health information of a decedent (with certain required Investigator representations).

11.3 Express Research Participant Authorization for Research

HIPAA requires that research participants provide specific permission – also known as ‘authorization’ - for their PHI to be used and/or disclosed in a research study. The research authorization required under HIPAA is distinct from, and required in addition to, a participant’s informed consent to participate in the research study; however, the authorization may be combined in the same document as the informed consent. By signing the informed consent and research authorization, a participant agrees to assume the potential risks (both physical and regarding the confidentiality of the participant’s health information) of the study, and authorize the use and disclosure of their PHI for the purposes of conducting the research.

HSL has a template research authorization form, but a research sponsor may also have its own research authorization template (collectively referred to herein as a “Research Authorization Form”). The template Research Authorization Form must be tailored by the Investigator and approved by the IRB before it is presented to the research participant(s) for review and signature. It is the responsibility of the Investigator to ensure that the completed Research Authorization Form covers the uses and disclosures necessary for the research study.

In general, an Authorization must be written in ‘plain language’ and include the following information:
• A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion;
• The names or other specific identification of the persons authorized to disclose and receive the information;
• A description of future research that sufficiently describes the purposes such that it would be reasonable for the individual to expect that the PHI could be used or disclosed for such future research;
• An expiration date or expiration event that relates to the individual or the purpose of the use or disclosure. An expiration date may be the end of the study, repository, database, or there may be no expiration date. An authorization may also state that it will remain valid unless and until it is revoked by the individual.
• The individual’s right to revoke the authorization in writing; any exceptions to the right to revoke the authorization and a description of how the individual may revoke the authorization or, if such information is included in the notice required by 45 CFR § 164.520, a reference to the covered entity’s notice. Individuals should be aware that revocation of an authorization does not always mean that their information may no longer be used in the research study or may no longer be used or disclosed for any other purpose. A covered entity may continue to use and disclose PHI that was obtained before the individual revoked authorization to the extent that the entity has taken action in reliance on the authorization.
• The ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the authorization; and
• The potential for information disclosed pursuant to the authorization to be subject to redisclosure by the recipient and no longer be protected by the HIPAA Privacy Rule.

The IRB may allow the use and disclosure of PHI for research purposes pursuant to a completed and signed Research Authorization Form. Permissible uses and disclosures are limited to those described in the signed Research Authorization.

An individual’s ability to participate in research-related procedures (i.e., in the course of a clinical trial) may be conditioned upon the individual’s agreement to sign the Research Authorization Form. However, in presenting the Research Authorization Form to prospective participants, researchers should never suggest that failure to sign the form limits the individual’s access to procedures that may be available outside the study.

11.4 Waivers of Research Participant Authorization

The IRB may allow the use and disclosure of PHI for research purposes absent individual authorization if the IRB grants a partial or total waiver of the authorization requirement. If the IRB grants only a partial waiver – that is, if it modifies or waives only some elements of the Research Authorization Form or waives the requirement for authorization for certain but not all research activities – the IRB must condition the use and/or disclosure of any PHI for research purposes on compliance with any authorization requirements not waived and as modified. For example, if the IRB grants a partial waiver of authorization to allow a researcher to obtain protected health information to recruit potential research participants, the researcher would still have to obtain authorizations from the subjects to use or disclose PHI for the study itself.

In order to grant a waiver of the HIPAA authorization requirement, the IRB must find that all of the following criteria are present:
1. The use or disclosure of health information involves no more than minimal risk to the individuals because:
   a. there is an adequate plan to protect the identifiers;
   b. there is an adequate plan to destroy the identifiers at the earliest opportunity, unless there is a health (i.e., individual care) or research justification for retaining the identifiers or their retention is required by law; and
   c. there are adequate written assurances that the health information will not be reused or disclosed to any other person or entity, except (1) as required by law, (2) for authorized oversight of the research project, or (3) for other research for which the use or disclosure of health information is otherwise permissible under the policy.
2. The research could not practicably be conducted without the waiver; and
3. The research could not practicably be conducted without access to and use of the health information.

If an Investigator intends to apply to the HSL IRB for a waiver of HIPAA-required authorization, they must complete the eIRB Form A – Request to Use/Disclosure Protected Health Information for Research.

External Investigators (non-HSL workforce members) requesting the use or disclosure of HSL resident/patient PHI may be permitted such information by the HSL Privacy Officer upon receipt of appropriate documentation of IRB waiver. Such documentation should include:
• the name of the IRB (not the names of individual members of the board);
• the date on which the waiver was approved;
• the signature of the IRB chair, or other member designated by the chair;
• a statement that the IRB has determined that the waiver satisfies the required criteria;
• a brief description of the protected health information that the IRB has determined is necessary for research purposes; and
• a statement that the waiver has been reviewed and approved under either normal or expedited review procedures and that all applicable procedures were followed.

If any such documentation is missing or inadequate, the Privacy Officer shall notify the Investigator and will not approve the requested uses or disclosures until the documentation is complete.

Note: A waiver of individual HIPAA authorization under this policy is not a waiver of the requirements of informed consent for the project or of any other consent required by HSL’s policies. The IRB may waive or alter informed consent requirements, but the IRB must review a request to waive or alter informed consent separately under criteria set forth in 45CFR46.116 and 45CFR46.117. Although evaluated distinctly, if the IRB has determined that a research project requires informed consent because the criteria for waiver are not met, it is unlikely that the criteria for waiver of HIPAA authorization are met (and vice versa).

11.5 Limited Data Sets/Data Use Agreements

HSL may allow, absent individual HIPAA authorization, the use and disclosure for research purposes a Limited Data Set (see definition in section 11.1) that includes a subset of the individual’s PHI that has been stripped of all direct identifiers, provided that all persons or entities using or receiving the Limited Data Set have signed a Data Use Agreement with HSL.

A member of HSL’s workforce (or a third party that has signed a Business Associate Agreement with HSL) may use HSL’s PHI to create a Limited Data Set to be used in research without individual authorizations, because such an activity is considered to be part of HSL’s health care operations.

Individuals seeking to use or disclose a Limited Data Set for research purposes (or seeking access to PHI to create a Limited Data Set, either on their own or using a contracted Business Associate) should make a request to the HSL Director of Research Informatics.

More information on Limited Data Sets and Data Use Agreements can be found on the Data Protection page of the Marcus Institute website.

11.6 De-Identified Information

The IRB may allow completely de-identified information to be used and disclosed for research purposes without restriction; no individual authorization is required. Information may only be considered completely de-identified when either: (1) a qualified statistician documents his or her determination that the risk of identification is very small, or (2) the information is stripped of all of the identifiers described in Section 11.1 of this policy. If the IRB has any doubts as to whether PHI has been completely de-identified within the meaning of this policy, the information should be treated as though it were not completely de-identified and neither used nor disclosed for research purposes without meeting another exception.

11.7 Review of Protected Health Information Preparatory to Research

The IRB may permit the use and disclosure of PHI to develop a research protocol or for similar purposes preparatory to research (e.g. to determine whether HSL has a sufficient number of prospective research participants that would meet the eligibility criteria for enrollment in a research study).
In order to permit a use or disclosure of PHI under this exception (i.e., absent individual authorization), the IRB must obtain representations from the Investigator that:

- the use or disclosure is sought solely to prepare a research protocol or for similar purposes preparatory to research;
- no researcher will remove any PHI from the covered entities’ premises in the course of the review; and
- the PHI for which use or access is sought is necessary for the research purposes.

During the preparatory review, those granted access may only record information in a form that is “de-identified” in accordance with this policy.

Treating physicians and other members of a patient’s treatment team are permitted to review their own patients’ health information to determine whether those patients might be eligible to enroll in a research study; such activity, although arguably preparatory to research, does not require the representations outlined herein. Treating physicians are permitted to contact their patients about and/or discuss with their patients available research options.

11.8 Use of Decedent Data

The HIPAA Privacy Rule protects the PHI of decedents for 50 years following the death of the individual. Investigators wishing to access/use the PHI of decedents within 50 years of the individual’s death must make the following representations to the HSL IRB (or Privacy Officer):

- The use or disclosure of the PHI is solely for research on the PHI of decedents;
- Documentation, at the request of the covered entity (HSL or an external institution) of the death of such individuals; and
- Confirmation that the PHI for which use and disclosure is sought is necessary for research purposes.

11.9 Minimum Necessary Standard/Requirements

As a general matter, the HIPAA Privacy Rule requires that the use and disclosure of PHI for research purposes must be the minimum necessary to accomplish the intended purpose of the use (e.g. only the information that is needed for the present use or disclosure should be made available by the health care provider or other covered entity), except for when the PHI is used or disclosed pursuant to a participant’s research authorization as described in Section 11.3. When reviewing representations associated with reviews preparatory to research (see Section 11.7) and/or research on decedents’ PHI (see Section 11.8), the IRB may rely on the representation that the PHI is necessary for the research purposes as satisfying the minimum necessary standard.

11.10 Participant Access Right to Protected Health Information during Research

HIPAA grants individuals certain rights to access their PHI maintained by covered entities. These rights apply generally to PHI collected or generated in the course of research, unless research participants are informed that their access rights will be temporarily limited during the course of the research and reinstated upon conclusion of the study. Therefore, in the event Investigators intend to limit participants’ access to their PHI (for example, in the context of a blinded clinical trial where participants may not know to which arm they have been randomized), this must be outlined clearly in the individual authorization signed by participants prior to the start of the research.
11.11 Accounting for Research Disclosures of PHI

Individuals have the right to an “accounting” of all disclosures of their PHI for research purposes in the six (6) years prior to the request, except disclosures made:
1. Pursuant to a research authorization;
2. To carry out treatment, payment or the general operations of HSL, including quality assurance/continuing quality improvement activities;
3. To the patient him or herself;
4. As part of a Limited Data Set.

Individuals interested in obtaining an accounting of disclosures of their PHI for research purposes must submit such requests to the HSL Privacy Officer. Investigators are required to maintain sufficient records of any disclosures of PHI for research purposes in order to assist HSL in responding to a request for such accounting. In the event a request for an accounting of disclosures is made by a research participant directly to a researcher or anyone else within the Marcus Institute, the Privacy Officer should be notified immediately.
12. **Populations Vulnerable to Coercion or Undue Influence and Special Protections**

As outlined in Section 2.2, as a general matter, the HSL IRB will not ordinarily review the following categories of research, absent special circumstances and preparation:

- Research involving pregnant women, fetuses, or neonates [45 CFR § 46.201-207 (Subpart B)]
- Research that plans to or is likely to involve prisoners [45 CFR § 46.301-306 (Subpart C)]
- Research involving children [45 CFR § 46.401-409 (Subpart D); 21 CFR § 50.50-50.56 (Subpart D)]

In the event that the HSL IRB is required review research involving the above populations, it has developed policies and procedures that are maintained under separate cover and available upon request to the IRB Director.

Under the Revised Common Rule at 45 CFR 46.111(a)(3) and (b), the regulations require that when the research participants are “likely to be vulnerable to coercion or undue influence, such as children, prisons, and individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these individuals.” Below, please find categories of such populations with which HSL Investigators are likely to conduct research.

12.1 **Research within the Jurisdiction of the Massachusetts Department of Mental Health (DMH) and the Department of Developmental Services (DDS)**

Under 104 C.M.R. § 31.00, et seq., DMH has the jurisdiction to review and approve any human research “related to” the Department, its facilities or programs in which its “clients” are proposed participants. Investigators whose research falls within the DMH’s jurisdiction must submit proposals to the DMH IRB, the Central Office Research Review Committee (CORRC), for approval.

DMH regulations (104 CMR § 31.01 et seq.) describe information Investigators must submit to the agency concerning such studies, and the standards governing review and approval of studies by the agency, which are very similar to the standards of review utilized by IRBs operating under the 45 CFR § 46. However, the regulations impose a few additional content requirements for informed consent forms for these studies, beyond those included in the 45 CFR § 46, such as: statements describing “the basis for selection of the subject”, and a statement indicating that participation in the study is not required of participants in order to obtain continued access to DMH services. Please see DMH regulations for specific information.

A similar system for State review of protocols exists under the jurisdiction of DDS. Please see the regulations under 115 CMR 2 and 115 CMR 10. If you have any questions regarding these regulations, please seek guidance from the HSL IRB Director and General Counsel and Chief Compliance Officer.

12.2 **Research with Individuals with Limited Decision-Making Capacity**

The HSL research subject population includes adults who have limited decision-making capacity due to illness, disability, or disease. Both HHS and FDA regulations require that informed consent be obtained for participation in research from the subject or their legally authorized representative (LAR). Assessing an individual’s capacity to consent to research, and engaging legally authorized representatives is covered in Sections 4.5 and 4.6.
12.3 **Employees, Fellows, Trainees, Students and Volunteers of HSL**

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

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

12.4 **Investigator Self-Experimentation**

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

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

12.5 **Certificates of Confidentiality**

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

Per NIH and PHS policy:

The recipient of a Certificate shall not:

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

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

Investigators conducting NIH supported research, per 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. As such, HSL Investigators should refer to the applicable policies on the Data Protection page of the Marcus Institute website.

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

FDA’s regulations, including those governing IRB review, informed consent and protection of human subjects, may apply to research sponsored or conducted by or at HSL. A sponsor or sponsor-Investigator, as defined below, should determine whether proposed research is subject to FDA regulation. When in doubt, a sponsor or sponsor-Investigator may consult the IRB. If FDA regulations apply to proposed research, the sponsor or sponsor-Investigator may be obligated to submit to FDA an Investigational New Drug (“IND”) or Investigational Device Exemption (“IDE”) application prior to the commencement of the research.

The following procedures describe the use of investigational drugs and devices and other FDA regulated products in research otherwise under the auspices of HSL.

13.1 Definitions

Clinical Investigation: Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA (i.e., it requires an IND or IDE to conduct the investigation), or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

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

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

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

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

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

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

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

Sponsor: For purposes of this Section 13, a person (or entity) who takes responsibility for and initiates, but does not actually conduct, a clinical investigation. An entity that uses one or more of its employees to...
conduct an investigation that it has initiated is a sponsor, not a sponsor-Investigator, and the employees are Investigators.

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

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

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

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

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

### 13.2 FDA Exemptions from IRB Oversight

The following categories of clinical investigations may be exempt from the requirements of FDA regulations for prospective 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 (see section 13.7), per 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, per 21 CFR §56.104(d). See Section 5.4 for the requirements and process for exempt research.

### 13.3 IND/IDE Requirements

Non-exempt clinical investigations reviewed and approved by the HSL IRB must comply with applicable FDA regulations, including 21 CFR Parts 50, 56, 312, and 812. Those regulations require, in part, that an IND or IDE, as applicable, be granted by the FDA in advance of shipping any investigational drugs or devices for use in the clinical investigation. These requirements do not apply to the practice of medicine, including the off-label use of an approved test article in the practice of medicine.

Investigators will be asked on the IRB application to indicate whether the proposed research involves drugs or devices. If so, they will be asked if there is an IND/IDE for the research, who is the holder of the IND/IDE (e.g., the sponsor or sponsor-Investigator, as applicable), and to provide documentation of the IND/IDE and assurances from the sponsor that the manufacture and formulation of investigational or unlicensed test articles to be used in the research conform to federal regulations. Specifically, the Investigator must provide the IRB with a copy of the letter from the FDA issuing the IND/IDE assignment.
for the clinical investigation. Documentation of the assurances from the sponsor regarding the manufacture of any investigational products could be in the form of a letter from the 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 one is not required. If the FDA has made any finding that an IND or IDE is not required, documentation of that finding must be provided to the IRB.

The IRB will review research involving investigational drugs or devices in accordance with the general requirements for review of human subjects research described in this Policy, including any specific FDA-requirements for the approval of FDA-regulated research at 21 CFR 56.111. The IRB is responsible for ensuring that for any clinical investigation involving a drug or device, the IRB considers and documents whether an IND or IDE is present or, if not, the rationale for why the research is exempt from such requirements.

13.4 Clinical Investigation of Drugs (IND Requirements)

In general, the requirements for an IND apply whenever any drug, whether approved or unapproved, is used in a clinical investigation, even when the drug is not “investigational” by definition (e.g., the study of an approved drug, whether to study its labeled indication to collect additional safety and efficacy data, or to study a new non-labeled use). For drugs, a clinical investigation of an approved, marketed drug may be exempt from the requirements for an IND (and 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. If the drug being studied is lawfully marketed as a prescription drug product, 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 subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent, per 21 CFR parts 56 and 50, respectively; and
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs, per 21 CFR 312.7.

There may be other circumstances in which an IND will not be required, such as clinical investigations of in vitro diagnostic biological products, drugs intended solely for tests in vitro or in laboratory research animals, and clinical investigations involving use of a placebo where the investigation does not require submission of an IND. The IRB will consider the applicability of the FDA’s IND requirements on a case-by-case basis in accordance with the process outlined herein.

13.5 Clinical Investigation of Devices (IDE Requirements)

When a device is being evaluated in the context of a clinical investigation for safety and effectiveness, the device is considered “investigational” and is subject to the FDA IDE requirements in 21 CFR 812, unless exempt. For devices, an IDE approved by the FDA may not be necessary if:

1. The research involves a non-significant risk device (NSR), in which case the device is “deemed” to have an approved IDE if all of the following requirements are met:
   a. The device is labeled in accordance with applicable FDA regulations, per 21 CFR 812.5;
b. The IRB approves the clinical investigation after considering the sponsor’s or sponsor-Investigator’s brief explanation of why the device is not a significant risk device (IRB approval must be maintained for the duration of the clinical investigation);

i. The FDA is the definitive arbiter of whether a device study is a significant risk (SR) or NSR, and the agency makes this determination when an IDE is submitted to it or if asked to make this determination by a sponsor, clinical Investigator, or IRB. If the FDA has determined that a study is NSR, the sponsor should inform the IRB, and the IRB will not need to undertake its own determination. If the FDA has not made an SR/NSR determination, it is the sponsor’s responsibility to make an initial determination. If the sponsor initially determines that a study is NSR, the sponsor must provide the IRB with an explanation and any information that may help the IRB evaluate the risk of the study. Such information may include a description of the device, reports of prior investigations with the device, the proposed investigational plan, and research participant selection criteria. For an SR medical device study, a sponsor must submit an IDE application to the FDA and obtain FDA approval of the IDE before the study can begin. If presented with an SR determination by a sponsor, the HSL IRB shall request from the sponsor a copy of the FDA’s approval or conditional approval letter to prove that the SR study has an FDA-approved IDE application in accordance with 21 CFR 812.30.

ii. If presented with an initial NSR determination by a sponsor, the HSL IRB shall review, at a convened meeting, this initial determination and the information provided by the sponsor. When the IRB is making its SR/NSR determination, the IRB should consider factors such as the sponsor’s explanation of the initial NSR determination; how the device is proposed to be used in the research; the nature of harm that may result from the use of the device; and if subjects may need to undergo additional procedures as part of the research (e.g., surgery), the potential harm that the procedures could cause. The HSL IRB may request additional information from the sponsor, as needed, to facilitate its risk determination.

iii. If the IRB determines that an investigation presented as involving an NSR actually involves a SR, the Investigator is responsible for notifying the sponsor of the IRB’s determination upon receipt of written notice. The Principal Investigator should provide the IRB with confirmation of this action. Such an investigation may not be reviewed through the expedited process and will not be permitted to begin without an IDE, granted in accordance with 21 CFR 812.30.

iv. The IRB must document in the minutes its rationale for classifying a device as either NSR or SR and will include in its communication of approval or disapproval to the Investigator its determination of whether the device presents a significant or non-significant risk. Where appropriate, relevant documentation to support the IRB’s determination, such as a copy of an IDE approval letter or an FDA NSR determination letter, also should be included in the IRB meeting minutes.

c. Each Investigator participating in the investigation must obtain and document informed consent from each subject, unless documentation is waived under 21 CFR 56.109(c);

d. The sponsor complies with the monitoring requirements in 21 CFR 812.46;

e. The sponsor maintains the records and makes the reports required under applicable FDA regulations and ensures that participating Investigators do the same; and

f. The sponsor complies with the FDA’s prohibitions against promotion and other practices in 21 CFR 812.7.

2. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976 when used or investigated in accordance with the indications in labeling in effect at that time;
3. The research involves a device, other than a transitional device, introduced into commercial distribution on or after May 18, 1976, that the 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 the 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 subject, 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 subjects 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); or

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.

13.6 Investigator Responsibilities

In addition to the many requirements described elsewhere in this policy, Investigators may have specific requirements related to the conduct of clinical investigations involving investigational drugs or devices, many of which are described in detail in this Section. Investigators may consult with the IRB if they have any questions regarding their obligations under applicable FDA regulations and guidelines.

1. **Conduct of Research.** The Investigator is responsible for ensuring that the research is conducted according to all applicable requirements, including the Investigator’s and/or Institution’s signed agreement with the sponsor, if applicable, the investigational plan, and any applicable FDA regulations, including the prohibitions on promoting or commercializing investigational products. As with all human subjects research, the Investigator is required to obtain approval from the HSL IRB prior to commencing the clinical investigation.

2. **Record Keeping.** Investigators are required to maintain all required records and prepare and submit all required reports, in accordance with FDA regulations (21 CFR Parts 312 and 812). Investigators working on FDA-regulated studies are strongly encouraged to keep all data, notes, and consent forms as “research records” that are separate from the medical records. Federal agencies such as the FDA and others have the authority to inspect medical records of patients or subjects involved in research studies over which these agencies exert jurisdiction. Because of the legal questions involved in federal access to information unrelated to research, Investigators should contact the IRB before showing medical records to any inspectors.

3. **Control of Test Article.** The Investigator is responsible for the control and accountability of all investigational drugs and devices used in research at HSL, which includes storage, security, dispensing, administration, return, disposition and records of accountability. The Investigator may only administer
the investigational drug or device to those subjects enrolled in the clinical investigation and under the Investigator or his/her designee’s supervision, unless special procedures and approvals for expanded access are followed and met (see Section 13.9). The Investigator may not supply an investigational product to any person not authorized to receive it. All drugs received from the manufacturer for a study must be stored in a locked environment under secure control with limited access. The Pharmacy, already the center for drug procurement, storage and inventory control, dosage formulation and packaging, distribution and drug information services for the Institution, serves as the central coordinating center for investigational drugs. The drug inventory supply for any clinical investigation shall be received in care of the Pharmacy for the Investigator. Exemptions from this policy must be approved through the Pharmacy and Therapeutics Committee. If the drugs are not stored in the pharmacy (pursuant to an exemption), the area used for storage must be within the Investigator’s control. All investigational drugs must be dispensed by the Pharmacy, which will dispense them only upon receipt of an order or prescription written and signed by the Principal Investigator or designee as indicated in the study protocol. The Investigator must complete and submit to the eIRB Form C - Drugs and Biologics’, which contains information on the plan for storage, security and dispensing of the drug prior to its approval of the study. Proper instructions on the use of the drug must be provided to the participants. A log must be kept by the Investigator to account for the receipt, use and/or dispensing of the drug and the disposition of remaining drugs at the conclusion of the investigation.

Excess drugs (including FDA-approved medicines, supplements, or vitamins) or devices that are not used in the research project must be either returned to the Sponsor, or to the Pharmacy for disposal. Drugs and devices used in research may not be provided to any person not authorized to receive these materials.

4. Sponsor-Investigators. When an Investigator files an IND or IDE, the Investigator is considered the sponsor of the clinical investigation and as such carries all of the FDA regulatory responsibilities and reporting obligations applicable to both the Investigator and sponsor as described in the FDA regulations. Investigators intending to hold INDs or IDEs will be asked to complete additional education and training on the applicable requirements for sponsor-Investigators and the IRB may periodically conduct random audits of Investigators holding an IND or IDE.

13.7 Emergency Use

13.7.1 Emergency Exemption from Prospective IRB Approval

FDA regulations permit investigational products to be administered to patients without prospective IRB approval for “emergency use” purposes, per 21 CFR 56.104(c). In order to qualify for this exemption, the following conditions must be present (in accordance with the definition of “emergency use”): (1) a human subject is in a life-threatening situation; (2) no standard acceptable treatment is available; and (3) there is not sufficient time to obtain IRB approval. Informed consent is required before the emergency use unless the conditions for exception (described below in Section 13.8.2) are met. The IRB must be notified within 5 working days when an emergency use occurs. Any subsequent use of the test article at the institution is subject to IRB review. This notification of the IRB must not be construed as an IRB approval. Expedited approval of emergency use is not permitted; either the IRB must convene and approve the emergency use or, if the conditions described herein are met, the use may proceed without IRB approval. The IRB Director or designee will review the notification report to verify that circumstances of the emergency use conformed to FDA regulations. To the extent a manufacturer requires documentation from the IRB prior to shipping a test article for emergency use, the IRB will issue an acknowledgment letter providing a written statement that the IRB is aware of the proposed use and considers the use to meet applicable FDA requirement. Such an acknowledgment letter must not be construed as an IRB approval.
13.7.2 Emergency Waiver of Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of a test article without prior 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:

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

If immediate use of the test article is, in the Investigator’s opinion, required to preserve the life of the subject, and 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 working days. The IRB must be notified, by submission of the certified writing described above, within 5 working days when an emergency waiver is used. The IRB Director or designee will review the notification report to verify that circumstances of the emergency waiver conformed to FDA regulations. The IRB may require that the Investigator inform the subjects or their legally authorized representatives about the subjects’ involvement in the emergency research after the fact.

13.7.3 Emergency Waiver of IND; Non-Enforcement of IDE in Emergencies

FDA regulations at 21 CFR 312.310(d) address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an expanded access IND (which submissions are discussed further below). The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an expanded access IND application. A request for such authorization may be transmitted to the FDA by telephone or other rapid communication means as outlined in the regulations. Following the emergency use, the Investigator must submit an expanded access application to the FDA within 15 days of FDA’s authorization of the use. Prospective IRB review of the emergency use is required unless the conditions for exemption are met (see Section 13.7.1). Informed consent is required unless the conditions for exemption are met (see Section 13.7.2).

Although Part 812 does not contain a similar regulatory waiver of the IDE process in emergency circumstances, the FDA has used its enforcement discretion to recognize the same process for investigational devices in various guidance documents based on the criteria for emergency use outlined in Section 13.7.1.

13.8 Treatment INDs and IDEs and Other Expanded Access

There are various ways in which patients who are not enrolled in an on-going clinical investigation (for example, because they are too sick to meet the eligibility criteria) may nonetheless gain access to investigational products for treatment purposes outside the context of the investigation. This can generally occur either during the course of the approved clinical investigation or following its conclusion but before the test article is approved for marketing.

FDA regulations (21 CFR 312.300 et seq. and 812.36) address the treatment use of investigational drugs and devices in patients (single or groups) for whom no comparable or satisfactory alternative therapy is available. Use of the investigational product for this purpose must meet all applicable FDA requirements. These products are not currently approved for marketing, but are intended to treat or diagnose a serious or
immediately life-threatening disease or condition and are either currently under investigation in a controlled clinical trial for the same use, or the clinical trials have been completed and the product is awaiting marketing approval. For these types of treatment uses of investigational products, prior FDA authorization is required in the form of an expanded access IND or treatment IDE, which can be sought either by the sponsor or by the treating physician directly. If the treating physician intends to apply for an expanded access IND or treatment IDE, the manufacturer should be contacted to determine whether the manufacturer would agree to amend an existing IND or IDE to permit treatment use or, if not, grant the treating physician a right to reference its existing IND or IDE. Treatment IND/IDE studies generally require prospective IRB approval and subject informed consent unless the conditions for exemption outlined in Sections 13.8.1 and 13.8.2 are met.

Licensed practitioners who receive investigational products under expanded access INDs and treatment IDEs are “Investigators” for purposes of applicable FDA regulations and are required to meet all applicable Investigator responsibilities.

There are other mechanisms through which patients not eligible to participate in a clinical trial (or who have completed participation in such a trial) may nonetheless have access or continued access to investigational products off-protocol (for example, open label extension protocols). These circumstances will be handled on a case-by-case basis, with consultation with the Director of the IRB and/or General Counsel and Chief Compliance Officer as necessary.

13.9 Use of Controlled Substances in Research

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

Investigators using Schedule I-V drugs in research are required to hold both a federal Drug Control Registration (DEA Form 225, Researcher), as well as Massachusetts Controlled Substance Registration (MCSR) with the Massachusetts Department of Public Health as a “researcher”.

Generally, licenses are (i) issued to an individual, who may authorize other individuals to operate under his/her license under certain circumstances; (ii) specific to drug schedules identified on the license, and further limited to specific drug codes applied for; and (iii) identify a specific location where the controlled substances are to be stored and must be amended when the location of storage changes.

The DEA will not grant an applicant a license until the applicant has already obtained a license from the MA DPH. Investigators using only Schedule VI controlled substances would not need to be registered with DEA, but would still need to hold a controlled substance researcher registration from the MA Department of Public Health.

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

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

13.10 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research involving subjects 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. HSL has not historically engaged in such research; if such research is ever proposed or planned, it will be done in accordance with applicable regulations.

13.11 Humanitarian Use Devices

In accordance with 21 CFR 814.124, treatment with a Humanitarian Use Device (HUD) is subject to full board initial and continuing review by the IRB. (Continuing review may be performed by an expedited review process unless the IRB determines that full board review should be performed.) The IRB is not required to review and approve individual uses of a HUD; it may approve use of a HUD without any further restrictions, use of the device under a specific protocol, or use of the device on a case-by-case basis. The IRB should ensure that the proposed treatment use of the device does not exceed the scope of the FDA approved indication.

At the time of review of a HUD for clinical use, the IRB will determine if written consent from participants for use of the HUD is necessary. Because the clinical use of a HUD in accordance with its approved labeling does not constitute research, informed consent is not required by FDA regulation. 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 (or may be administered outside of its approved indications for use). In this instance, if possible given the emergent nature of the use, concurrence must be obtained from the IRB Chair, informed consent must be obtained from the patient or legally authorized representative, and an independent assessment must be performed by an uninvolved physician, as well as authorization from the Humanitarian Device Exemption (HDE) holder in the case of an off-label emergency use. The physician 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. Additionally, in the case of emergency off-label use, the treating physician should submit a follow-up report on the patient’s condition and information regarding the patient protection measures taken to the HDE holder, who would then submit this report to the FDA as an amendment to the HDE. Even when an emergency does not exist, a treating physician may administer a HUD off-label if the physician determines that there is no other alternative device to treat the patient’s condition, so long as the same patient protection measures are taken.

It is the responsibility of the treating physician 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. Physicians and Investigators are reminded that Humanitarian Device Exemptions are generally
for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application. If Investigators seek to conduct a clinical investigation on an off-label use of a HUD or to collect safety and efficacy data in support of an application for PMA, a separate IDE is not required; the investigation may be conducted under the existing HDE. However, IRB approval and informed consent are required in accordance with 21 CFR Parts 50 and 56.

13.12 Additional Considerations for FDA-Regulated Research

1. The informed consent must notify subjects that their medical records may be subject to review by the IRB, agents of the FDA and, in some cases, by agents of the commercial sponsor.
2. When there is a commercial sponsor, indemnification of HSL by the Sponsor is required.
3. Sponsor reporting forms should be modified where possible so that no names, initials or other identifiers are used when communicating research results. Separate research protocol numbers should be used to identify individual participants and only the Investigators should have the means to link the code numbers to identifiable patients.
14. Research Records Management

HSL and its Investigators have legal, institutional and ethical obligations to manage and retain records of research conducted at HSL. This section pertains to Investigator responsibilities in maintaining active study documentation as well as record retention of completed projects. Regardless of whether a study is ongoing or completed, Investigators are responsible for storing study documentation securely to preserve the integrity of the records and ensure the confidentiality of the data.

Study documentation may be collected, recorded and stored in physical (paper) or electronic form. Access to study documentation should be limited to study staff. Physical (paper) records should be stored in a secure area, such as in a locked file cabinet. Electronic records must be stored on HSL-compliant computers or mobile devices or other internally hosted services. Investigators must follow HSL IT and Marcus Institute requirements to safeguard electronic protected health information (ePHI) and other study data maintained electronically.

14.1 Definitions

Research records are recorded research information, data and materials (including photographs, videos, website content, electronic mail, budgets, databases and datasets, etc.) that are created or acquired in the process of performing research, regardless of sponsorship. Research Records include documents, materials, information and written correspondence that relate to the administration and financial management of research, reporting of research results, or sponsored award applications, as well as the record of all data or results that embody the facts resulting from scientists’ inquiries, including, but not limited to, research proposals, laboratory records, both physical and electronic, progress reports, abstracts, theses, oral presentations, internal reports, presentations, and journal articles at all stages of development.

14.2 Active Study Files

The Harvard Catalyst Regulatory Group has developed a Regulatory Binder, which details the materials that Investigators are required to maintain per federal regulations, and general guidance pertaining to document organization in human subject research. Investigators are advised to review the Regulatory Binder, and to maintain their study documentation accordingly. Maintaining study documentation according to the Regulatory Binder guidance will allow for optimal organization and regulatory compliance, and will aid the IRB and federal authorities in the event of an audit or quality assurance review.

14.3 Inactive File Record Retention

Investigators are required to adhere to the HSL Record Management, Retention, Disposition and Destruction Guidelines, which are consistent with the record retention policy outlined herein, as well as the Marcus Institute Record Retention Policy.

Note: Minimum record retention standard set by DHHS [45 CFR § 46.115(b)] and FDA [21 CFR § 56.115(b)], requires Investigators to maintain complete study records for three years following either (a) final reporting to the research sponsor, (b) final financial close-out of a sponsored research award, or (c) final publication of research results, whichever is later. Despite the HSL, DHHS and FDA record retention guidelines the federal government has a six-year (and under some circumstances, up to ten-year) period from the time of any violation of applicable federal false claim laws within which it may seek to reclaim federal grant funds and to assess possible additional penalties for misuse of federal funds. Therefore, HSL has set its record retention policy to seven years, as outlined below.
Research Records should be retained, generally, for a period of no fewer than seven (7) years after the end of a research project or activity.* For this purpose, a research project or activity should be regarded as having ended after (a) final reporting to the research sponsor, (b) final financial close-out of a sponsored research award, or (c) final publication of research results, or (d) cessation of academic or scientific activity on a specific research project, regardless of whether its results are published, whichever is later. Please note that research related financial and administrative records need only to be kept for 7 years from the final filing of the final financial close-out report.

*The seven (7) year period is based on the six (6) year period within which the federal government may seek to reclaim federal grant funds and to assess possible additional penalties for misuse of federal funds, plus a one year period to assure that any annual records destruction would not unintentionally include records during the sixth year of their existence.

The retention of research records includes the materials listed in Section 14.1, which is inclusive of important written correspondence (including mail and electronic mail, and copies of reports, analyses and progress reports) related to the research. The scope of the correspondence that should be retained should be sufficient to enable an independent party reviewing that correspondence to identify and understand primary findings, major events, and major strategic decisions or judgments made in the course of that research.

14.4 Regulatory Document Files

Regulatory documents that should be maintained on file for a particular research study depend upon the nature of the involvement of human subjects and applicable regulations (e.g., HHS, FDA, etc.) and the nature of the involvement of human subjects. Regulatory document files serve as a central location for maintaining study management documents that demonstrate compliance with applicable regulations, and institutional policies and procedures. A separate regulatory document file should be maintained for each study.

14.4.1 All Studies Involving Human Subjects

Investigators should maintain the following study-specific documents for every research study that involves human subjects:

1. A complete history of HLS IRB submissions and correspondence from initial application through study close out, including, when applicable, but not limited to:
   - eIRB application forms
   - Protocol
   - Consent Form
   - Recruitment materials
   - Any other documents approved by the HSL IRB
   - HSL IRB review letters
   - Investigator response to review letters
   - Any other correspondence between investigator and the HSL IRB.
   Note: Records of all eIRB submissions and related IRB review notification letters created and submitted after July 2015 are maintained in the eIRB system, with limited exceptions.
2. Sample case report forms (CRFs) and/or data collection forms
3. Completed study management logs or equivalent documentation of the following:
   - Delegation of responsibility / signature log
• Enrollment/health/medical records/excess human materials (for studies limited to accessing individually private information or samples)
• Monitoring activities
• Protocol deviations and unanticipated problems including adverse events
4. Correspondence and/or communications with study sponsor, funding agency, regulatory agencies, research collaborators (e.g., data use agreements, materials transfer agreements, etc.)
5. Financial disclosure forms submitted by study staff responsible for the design, conduct or reporting of the research.

14.4.2 Studies Involving Interventions or Interaction with Subjects

In addition to documents 1-5 above, Investigators should maintain the following documents for studies that involve an intervention or interaction with subjects:

1. Completed study management logs or equivalent documentation of the following, as applicable:
   • Pre-screening
   • Adverse events
2. Study staff qualifications
   • CVs of all study staff, dated
   • Current licensure and board certifications of professional staff
   • Safety or other training (e.g., infection control, laser safety, CITI, etc.)
   • Study specific training
3. Clinical laboratory certification (e.g., CLIA/CAP certificate) and normal reference ranges, and research laboratory director’s CV, when applicable.
4. Correspondence and/or communications with collaborating sites (multi-site research)
   Note: Study staff CVs, professional study staff licensure and board certifications, safety or other training and laboratory certification and normal reference ranges that support more than one study may be filed centrally for a research group/department.

14.4.3 Studies Involving FDA Regulated Drugs/Biologics or Medical devices

In addition to documents 1-9 above, Investigators should maintain the following documents for studies of FDA-approved or unapproved (investigational) drugs/biologics or FDA-approved/cleared or unapproved (investigational) medical devices:

1. Product information, to include, when applicable:
   (a) FDA-approved drugs/biologics or approved/cleared medical devices
      • Drug package insert
      • Device manual / Instructions for Use
   (b) IND drugs/biologics or IDE medical devices
      • Investigator’s Brochure (IB)
      • Device information / Report of prior investigations
2. FDA Forms, Submissions and Correspondence
   (a) IND/IDE Clinical Investigators (IND/IDE held by company, NIH or other entity)
      • Form FDA 1572/Statement of Investigator (IND Investigator)
      • Investigator’s Agreement (IDE Investigator)
   (b) Sponsor-Investigators (IND/IDE held by Investigator)
      • IND/IDE submission
      • IND protocol amendments / IDE supplements
      • IND/IDE safety reports
• IND/IDE annual reports
• IDE updated list of Investigators
• Form FDA 1571/IND Application
• Form FDA 3455/Disclosure: Financial Interests and Arrangements of Clinical Investigators
• Form FDA 3674/Certification of Compliance, with Requirements of ClinicalTrials.gov

3. Drug/device accountability, to include, when applicable, records of:
   • Shipping and receipt
   • Dispensing to subjects
   • Return of drug/medical device by subjects
   • Return of drug/medical device to sponsor
   • Destruction of drug/medical device, when destroyed at the investigative site

Note: The HRC pharmacy will maintains these records for HSL drug studies, however Investigators should provide the pharmacy with the appropriate log to use (the IRB office has drug/device template logs available, in the event that a log is not provided by the Sponsor). When someone other than the investigator maintains information about medical device accountability, this must be documented in a signed and dated note-to-file.

14.4.4 Research Participant Files

Investigators should maintain the following study-specific documents in a separate file for each research participant or legally authorized representative who provides informed consent, as applicable:
   • All original signed and dated consent forms
   • Documentation of informed consent when written informed consent is waived
   • Documentation of informed consent when informed consent is provided verbally
   • Documentation of subject eligibility and study procedures
   • Case report forms and data collection forms, signed, dated and completed
   • Instruments, questionnaires, diaries, or other documents completed by study participants and/or study staff
   • Correspondence, emails or phone calls to research participants.

Note: Research participants cannot request that study data be “deleted” or “erased” once it has been collected.

14.5 Access to Research Records by the IRB, Federal Agencies, and Sponsors

Research records must be available for inspection by the IRB, federal agencies with jurisdiction over the research (e.g. DHHS/OHRP, FDA) and the study sponsor, as applicable and if so requested. Investigators and research staff must make research records available to HSL administration as soon as possible upon request so that it may respond to federal audits or other official requests, respond to subpoenas or other document demands, and conduct other internal and external oversight activities.

14.6 Access to Research Records by Investigators Leaving (or who have left) the Institution

When an Investigator leaves HSL (e.g. to move to another institution, or retirement), his/her original research records must be retained at HSL. See Section 3.1 for more complete information.
15. Information for Prospective, Current Research Participants and Family Members

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

15.1 Research Participant Rights

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

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

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

15.2 Questions, Complaints or Concerns

From time to time, research participants, family members, HSL employees and community members may have questions, concerns or complaints about research (including new, ongoing, or previously conducted research) conducted at HSL or by HSL Investigators or employees. The following individuals may be contacted to discuss these issues in a confidential manner:

- IRB Director: 617.971.5415
- IRB Chair: 617.678.7592
- VP for Research Administration: 617.971.5351
- General Counsel and Chief Compliance Officer: 617.971.5219
The above-listed individuals may take down the caller’s name and contact information, or if the caller does not wish to be identified, notes will be taken on the incident or issue, and follow-up will occur with the Investigator.

Individuals may also call the Healthcare ValueLine at 1.800.273.8452, which is available 24 hours a day, 365 days a year. When an individual calls the Healthcare ValueLine, a trained Communications Specialist answers the call, makes notes of the concern, and prepares a report that is forwarded to the Compliance Officer for review, investigation, and response. Callers are not required to identify themselves, but may do so if they feel comfortable.

Depending on the nature of the call, the callers may be advised to contact the Investigator or his/her research personnel directly, or the Compliance Officer may act as the liaison between the two parties. If a serious allegation is made against the Investigator or his/her research personnel, the allegation will be treated in the manner outlined in Section 9 of this policy document.

15.3  Research Resources for Prospective, Current Research Participants and Family Members

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

- Community Connect to Research: [http://hcfama.org/blog/community-connect-research-linking-you-world-health-information-and-research-0](http://hcfama.org/blog/community-connect-research-linking-you-world-health-information-and-research-0)
Addendum 1 - Definitions for HSL IRB Policies and Procedures
(Definitions are those of DHHS, unless otherwise specified)

Adverse Event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Adverse events encompass both physical and psychological harms. See Section 8 for more details.

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

Clinical trials of experimental drugs, treatments, devices or behavioral interventions may proceed through four phases:
- **Phase I** clinical trials are done to test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g. determine a safe dosage range, and identify side effects). These trials are often done in healthy volunteers.
- **Phase II** clinical trials are done to study the biomedical or behavioral intervention in a larger group of people (several hundred), usually with the target disease or condition, to determine efficacy and to further evaluate its safety.
- **Phase III** studies are done to study the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- **Phase IV** studies are done after the intervention has been approved to market. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Engaged in Human Research: HSL is engaged in non-exempt human subjects research when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

Human Research: Any activity that either:
- Meets the DHHS definition of “Research” and involves “Human Subjects” as defined by DHHS (“DHHS Human Research”); or
- Is “Research” as defined by FDA and involves “Human Subjects” as defined by FDA (“FDA Human Research”).

Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information of identifiable biospecimens.
- **Intervention** includes both physical procedures by which information or biospecimens are gathered (e.g. venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.
- **Interaction** includes communication or interpersonal contact between investigator and subject.
- **Private Information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been
provided for specific purposes by an individual and the individual can reasonably expect will not be made public (e.g. a medical record).

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

**Human Subject as Defined by FDA:** An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. A human subject includes an individual on whose specimen (identified or unidentified) a medical device is used.

**Investigator:** Anyone involved in the design, conduct, or reporting of the research. For more information on the roles and responsibilities of investigators and research personnel, see Section 3.

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

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

**Principal Investigator:** A Principal Investigator (PI) is the individual who is responsible and accountable for conducting the research. The PI assumes full responsibility for the research procedures performed on participants, and is responsible for the scientific and technical direction of the project, and the integrity of the research data and results. For more information on the role and responsibilities of PIs, see Section 3.

**Research:** A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

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

- The use requires prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act as a use of a drug other than the use of an approved drug in the course of medical practice (i.e., an IND is required in order to receive and use the drug for clinical investigation purposes);

- The use requires prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act as an activity that evaluates the safety or effectiveness of a device (i.e., an IDE is required in order to receive and use the device for clinical investigation purposes);

OR

- Prior submission is not required, however the results of the experiment 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.
Addendum 2 – HSL IRB SOPs for Subparts B, C and D

1.1 Application of Subparts B, C and D to Human Subjects Research at HSL

1.2 Application of Exemption Criteria for Subparts B, C and D

Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) Subpart B. Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.

(2) Subpart C. The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

(3) Subpart D. The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met.

- Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed.
- Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

1.3 Pregnant Women, Neonates, and Fetuses

There are both Federal and Commonwealth of Massachusetts requirements for research with pregnant women and fetuses.

1.3.1 Federal Regulations Involving Pregnant Women and Fetuses

Under 45 CFR § 46.204, research involving pregnant women or fetuses may be conducted if all of the following conditions are met:

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

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater that minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, the pregnant woman’s consent is obtained in accord with the informed consent provisions of Subpart A of 45 CFR § 46;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of Subpart A of 45 CFR § 46, except that the father’s consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
(f) Each individual providing consent under paragraph (d) or (e) above is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children, as defined in 45 CFR § 46.402(a), who are pregnant, assent and permission are obtained in accord with the provisions of Subpart D of 45 CFR § 46; (NOTE: in MA an individual is automatically not a child for purposes of giving consent to medical procedures if she is pregnant or believes herself to be pregnant (MGL Ch. 112, s. 12F), therefore this requirement will never be triggered in MA, because if pregnant the individual qualifies as an adult and full consent is required).

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

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

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

1.3.2 Massachusetts Law Involving Fetuses in Research

Experimentation on human fetuses is also regulated under Massachusetts law, MGL Chapter 112C, § 12J(a), which states in part:

I. No person shall use any live human fetus whether before or after expulsion from its mother’s womb, for scientific, laboratory, research or other kind of experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother’s womb, provided that in the best medical judgment of the physician, made at the time of the study, said procedures do not substantially jeopardize the life or health of the fetus, and provided said fetus is not the subject of a planned abortion. . . . This section shall not prohibit or regulate diagnostic or remedial procedures the purpose of which is to determine the life or health of the fetus involved or to preserve the life or health of the fetus involved or the mother involved.

II. No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided, however, that such consent shall not be required in the case of a routine pathological study.

III. No person shall perform or offer to perform an abortion where part or all of the consideration for said performance is that the fetal remains may be used for experimentation or other kind of research or study.

IV. No person shall knowingly sell, transfer, distribute or give away any fetus for a use which is in violation of the provisions of this section.

For the purposes of this section, a fetus is a live fetus when, in the best medical judgment of a physician, it shows evidence of life as determined by the same medical standards as are used in determining evidence of life in a spontaneously aborted fetus at approximately the same stage of gestational development… [Also,] for the purposes of this section, "fetus" shall include a neonate and an embryo, but shall exclude a pre-implantation embryo or parthenote as defined in section 2 of chapter 111L and obtained in accordance with said chapter 111L.

The Massachusetts statute includes criminal penalties, but states that those who have performed a procedure that allegedly violates the statute’s provisions will not be held liable if: (i) the procedure received the written approval of a duly appointed IRB; and (ii) at the time the procedure was performed, there was not an outstanding court judgment that the procedure violated the statute. The IRB’s written approval must state specifically that the procedure does not violate the provisions of the statute and must set forth a reasonable basis for this conclusion. The written approval must contain a detailed description of the procedure and must be maintained as a "permanent record" of the IRB or the institution for which it acts. A copy of the written approval must be filed with the office of the District Attorney for the county in which the IRB’s institution is located, and shall be available for public inspection at all times. MGL Chapter 112C, § 12J(a)(V-VII). IRB members are themselves immune from liability under the statute if they acted in good faith in concluding that the procedure was lawful. MGL Chapter 112C, § 12J(a)(VI).
1.3.3 Neonates

45 CFR § 46.205 provides as follows:

(a) Neonates of uncertain viability and nonviable 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 under paragraph (b)(2) or (c)(5) of 45 CFR § 46.205 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; and
   (4) The requirements of paragraph (b) or (c) of 45 CFR § 46.205 have been met as applicable.

(b) Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by 45 CFR § 46.205 unless the following additional conditions are met:
   (1) The IRB determines that: (i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
   (2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent’s legally authorized representative is obtained in accord with Subpart A of 45 CFR § 46, except that consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) After delivery a nonviable neonate may not be involved in research covered by 45 CFR § 46.205 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 Subpart A of 45 CFR § 46, except that the waiver and alteration provisions of § 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate 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 of both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

(d) 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 45 CFR § 46 Subparts A and D.

1.3.4 Confidential Birth Information

MGL Chapter 111, § 67E requires physicians to report diagnoses of congenital anomalies and birth defects to the Department of Public Health (DPH). 105 CMR § 302.070 provides a mechanism by which researchers may request access to use this confidential birth information for research with the purpose of reducing morbidity and mortality in Massachusetts. Researchers must submit to DPH an application that includes: the purpose and design of the study, its public health benefits, its relationship to the DPH’s goal of reducing morbidity and mortality, the data requested, a justification for the data request, a description of the extent to which the study involves “contact with the data subjects,” a description of the extent to which
informed consent will be obtained from the participants, information regarding IRB review and approval of the project, proposed measures to preserve the confidentiality of the data, and the names and titles of all persons who will access the data requested. Investigators also must submit to DPH copies of consent forms, questionnaires or telephone interview scripts, their filings with an IRB, the IRB’s written determinations, and their CVs. 105 CMR § 302.070(B) and (C). Investigators’ use of confidential birth information released by the DPH is subject to the terms and restrictions set forth in 105 CMR § 302.080. Thus, in addition to following IRB policies, investigators also must comply with DPH IRB requirements.

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

45 CFR § 46.206 provides as follows:
(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state or local laws and regulations regarding such activities. (See 12.1.2 regarding applicable Massachusetts law.)
(b) If information associated with material described in paragraph 45 CFR § 46.205(a) is recorded for research purposes in a manner that could identify living individuals, either directly or through identifiers linked to those individuals, then those individuals are human subjects and all pertinent subparts of 45 CFR § 46 and this policy are applicable.

1.3.6 Research not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates

Under 45 CFR § 46.207, where the IRB does not believe that the proposed research meets the requirements of 45 CFR § 46.204 or § 46.205, but does believe that it 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, it may refer the protocol to the DHHS for review. The research may proceed only if the Secretary of DHHS, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, ethics, law) and following an opportunity for public review and comment (including a public meeting), determines either: (1) that the research in fact satisfies the conditions of 45 CFR § 46.204; or (2) the following:
(a) 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;
(b) the research will be conducted in accordance with sound ethical principles; and
(c) informed consent will be obtained in accord with the informed consent provisions of 45 CFR § 46 Subpart A and any other applicable subparts.

1.4 Prisoners

Under 45 CFR § 46, Subpart C, prisoners who participate in research are afforded additional safeguards because their incarceration might affect their ability to make truly voluntary and un-coerced decisions. These additional protections apply not just to individuals who are prisoners at the time they are enrolled in a study, but also to those who become incarcerated during the course of a study.

A prisoner is defined as: “any individual involuntarily confined or detained in a penal institution.” The definition includes “individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial or sentencing.” 45CFR§ 46.303(c). The IRB interprets this definition to include individuals who are sent by court order to alcohol/drug rehabilitation facilities.
1.4.1 Additional IRB Composition Requirements

45 CFR § 46.304 (a) and (b) requires that, in addition to meeting the composition requirements set forth in 45 CFR § 46.116 and 46.107, if the IRB reviews research involving prisoners as research participants then it must also meet the requirements set forth below. These requirements apply to all aspects of review, including initial review, continuing review, review of study amendments, and review of reports of unanticipated problems involving risks to the participants:

(a) A majority of the IRB members (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.

(b) At least one IRB member 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.

1.4.2 Additional Issues for Consideration by the IRB

Under 45 CFR § 46.305(a), where prisoners are involved in potential research, the IRB may approve such research only if it finds, in addition to other approval requirements, that:

(1) The research under review represents one of the categories of research permissible under 45 CFR § 46.306(a)(2) set forth below in Section 12.2.3;

(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 subjects 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 subjects 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 subject population;

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

HSL is required to certify to the DHHS Secretary that the HSL IRB has made the required findings. HSL, or the institution to which HSL has ceded review if applicable, must send to OHRP a certification letter to this effect, which should also include the name and address of the institution and specifically identify the research protocol in question and any relevant HHS grant application or protocol. Research involving prisoners as participants may not proceed until OHRP issues its approval in writing to the institution on behalf of the Secretary under 45 CFR § 46.306(a)(2).
1.4.3 Permitted Categories of Research Involving Prisoners

Under 45 CFR § 46.306, biomedical or behavioral research conducted or supported by DHHS may involve prisoners as participants only if: the institution responsible for the conduct of the research has certified to the Secretary of DHHS that the IRB has approved the research under the standards set forth in 45 CFR § 46.305; and in the judgment of the Secretary of DHHS, the proposed research involves solely the following:

1. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
2. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
3. Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of DHHS has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the Secretary’s intent to approve such research; or
4. Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of DHHS has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the Secretary’s intent to approve such research.

Unless it meets the criteria set forth above, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as research participants. In determining whether the proposed research meets these criteria, the IRB must apply the definition of “minimal risk” set forth in 45 CFR § 46.303(d), rather than the definition set forth in 45 CFR § 46.102(i). The applicable definition of “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.” 45 CFR § 46.303(d).

1.4.4 Expedited Review Procedures

Ordinarily, the IRB will not expedite its review of research involving prisoners, however expedited review procedures are permitted under 45 CFR § 46.110 and 21 CFR § 56.110 for minor changes in approved research and for certain kinds of research involving no more than minimal risk. As noted above, with respect to research involving prisoners, the IRB must apply the definition of “minimal risk” set forth in 45 CFR § 46.303(d).

1.4.5 Exempt Research with Prisoners

The exemptions set forth in 45 CFR § 46.101(b) do not apply to research involving prisoners. 45 CFR § 46.101(i), FN1.

1.5 Children

45 CFR § 46 Subpart D affords special protections for children involved in research to prevent any unnecessary risk or harm. Under 45 CFR § 46.402(a), children are defined 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." Massachusetts law contains a number of provisions that define minors and the limited number of circumstances under which children who have not
reached majority may consent to receive medical care, or to participate in research, and circumstances and conditions under which the child’s parents or legal guardians may consent on their behalf. These provisions are outlined below. For research conducted outside of Massachusetts, the IRB will consult the Chief Compliance Officer/General Counsel to understand and apply the applicable law of the jurisdiction in question.

**Age of majority.** Eighteen is the age of majority in Massachusetts (M.G.L. c. 231, § 85P). When a person turns 18, s/he is considered to be an adult under Massachusetts law. (Buying and consuming alcohol, however, are two activities that are not legal until a person turns 21 in Massachusetts.)

Massachusetts law recognizes two instances when children under the age of 18 may have the legal capacity to consent to medical treatment. These are the **emancipated minor** and **mature minor rules**. Note that these rules concern individuals in their capacity as patients, not as participants in research, and also that they apply only to persons in Massachusetts. These rules would not apply, for example, to research participants living in a foreign country or in another state, although that other jurisdiction might have analogous rules.

**Emancipated minor.** A patient under 18 years of age may consent to treatment of any kind, except abortion, and may authorize the release of his or her medical records if s/he is: (a) married/widowed/divorced, (b) a parent (in which case the patient may also consent on behalf of the child’s medical or dental care), (c) a member of the armed forces, (d) living apart from parents and managing his or her own finances, or, in the case of a female, (e) pregnant or believes herself to be pregnant. M.G.L. c. 112 § 12F. A female under the age of 18 may consent to an abortion if she is or has been married. Otherwise, consent must be obtained from her parent(s) or the procedure must be authorized by court order. M.G.L. c. 112 § 12S. Further, patients under 18 years of age may consent to treatment and may authorize the release of their medical records relating to: diseases dangerous to the public health, drug dependency (but not alcohol dependency), and pregnancy (but not abortion, except in the case of those who had married).

**Mature minor.** Under Massachusetts case law, students under the age of 18 who are not emancipated under M.G.L. c. 112, § 12F, can, in certain circumstances, nevertheless consent to treatment and control access to their medical records. In such cases, the clinician proposing to provide the treatment may determine that the patient is a mature minor capable of consenting to treatment. To reach this determination, the clinician must conclude that the minor is capable of giving informed consent to the treatment; and that it is in the best interest of the minor not to notify his or her parents of the intended medical treatment. In general, where a minor has the capacity to consent to medical treatment, that minor also has the capacity to control his or her medical records, including releasing them to others, such as researchers.

**Parents or Guardians of minor children.** In general, and as more fully explained below, parents and guardians may provide consent to participation in research for their minor children or wards. The definition of who is a parent or guardian differs in some respects under federal and Massachusetts laws. The Massachusetts Uniform Statutory Will Act (the “Will Act”) indirectly defines “parent” in its definition of “child.” See M.G.L. c. 191B, § 1(1). Under this law, the “parent” is the biological or adoptive mother or father of a child. However, a father of a child who is not married to the child’s mother may not always be considered a parent; his status would depend on whether he openly treats the child as his offspring or on whether a court has made a paternity determination. Under the Will Act, the term “parent” does not include step-parents who have not formally adopted the child, foster parents, grandparents or other relatives. Id. In general, the term “guardian” is widely understood to mean a person lawfully invested with the power, and charged with the duty, of taking care of and managing the property and rights of someone who is considered incapable of administering his or her own affairs. This definition includes a person who legally has responsibility for the care and management of the person or estate or both of a child during his or her minority. Parents are usually considered the guardians of their minor children under Massachusetts law.
For example, with respect to children, the Department of Developmental Services defines “guardian” in its regulations concerning research as “a natural or adoptive parent, or the individual or agency with legal guardianship of the person.” 115 CMR 10.02.

Legal guardianship in Massachusetts usually is created through a court process, most often through the Probate Court, M.G.L. c. 201 § 2, although parents may designate another adult to be a guardian without having to invoke a court proceeding. This kind of guardian, once appointed, is also referred to as a “standby proxy,” whose authority becomes enforcible when the parent dies, becomes incapacitated or is unavailable to care for the child. M.G.L. c. 201 §§ 2B – 2D. The Department of Children and Families (DCF) or other state agencies may become the legal guardian of children it takes into custody. The IRB will make a determination based on the risk/benefits to determine whether to accept DCF, or other agency consent for children in their custody.

In general, a parent or legal guardian is considered under federal policy to be the legally authorized representative of a child, and thus may consent to the child’s participation in a research project. Thus, for a child participant in research, a parent or guardian acting as a legally authorized representative can give permission (consent) on behalf of the child to participate in research. As discussed above, an exception to this general rule is where the research involves medical treatment and the child has the capacity to consent under the emancipated minor or mature minor rules.

These issues are complicated and should be reviewed in-advance with the IRB Director and Chief Compliance Officer/General Counsel.

1.5.1 Research Not Involving Greater than Minimal Risk

Under 45 CFR § 46.404, where the IRB has found that the proposed research presents no greater than minimal risk to the children, it may approve the research only if it also finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR § 46.408. (Note that under 45 CFR § 46.408(b), the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR § 46.405 even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.)

1.5.2 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child participants

Under 45 CFR § 46.405, where the IRB has found that the proposed research presents more than minimal risk to the children but involves either an intervention or procedure that holds out the prospect of direct benefit for the individual participant, or a monitoring procedure that is likely to contribute to the participant’s well being, it may approve the research only if it also finds that:

a) the risk is justified by the anticipated benefits to the subjects;

b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

c) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR § 46.408.

(Note that 45 CFR § 46.408(b), the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR § 46.405 even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for care and custody of the child.)
1.5.3 Research involving greater than minimal risk and no prospect of direct benefit to the individual child participants, but likely to yield generalizable knowledge about the participant’s disorder or condition

Under 45 CFR § 46.406, where the IRB has found that the proposed research presents more than minimal risk to the children and involves either an intervention or procedure that does not hold out the prospect of direct benefit for the individual participant, or a monitoring procedure that is not likely to contribute to the participant’s well-being, it may approve the research only if it also finds that:

a) the risk of the research represents a minor increase over minimal risk;
b) the intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations;
c) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and
d) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR § 46.408.

(Note that, under 45 CFR § 46.408(b), where research to be conducted under 45 CFR § 46.406, and permission is to be obtained from parents, both parents must give their permission unless either: one parent is deceased, unknown, incompetent, or not reasonably available, deceased; or only one parent has legal responsibility for the care and custody of the child.)

1.5.4 Research not otherwise approvable that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children

Under 45 CFR § 46.407, where the IRB does not believe that the proposed research meets the requirements of 45 CFR §§ 46.404, 46.405, or 46.406, but does believe that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to DHHS for review. The research may proceed only if the Secretary of DHHS, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR § 46.404, § 46.405, or § 46.406, or (2) the following:

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

(Note that, under 45 CFR § 46.408(b), where research to be conducted under 45 CFR § 46.407, and permission is to be obtained from parents, both parents must give their permission unless either: one parent is deceased, unknown, incompetent, or not reasonably available, deceased; or only one parent has legal responsibility for the care and custody of the child.)

1.5.5 Parental/Guardian Permission Requirements

Under 45 CFR § 46.408(b), for research involving children, the IRB must determine, in accordance with and to the extent required by 45 CFR § 46.116, that adequate provisions are made for soliciting the permission of each child’s parents or guardian. As noted above, for research conducted under 45 CFR §§ 46.404-405 (minimal risk), the IRB may find that the permission of one parent is sufficient. Where research is to be conducted under 45 CFR §§ 46.406-407 (greater than minimal risk), and permission is to be obtained from parents, both parents must give their permission unless either: 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.

Under 45 CFR § 46.408(c), in addition to the requirements for waiver set forth in 45 CFR § 46.116, if the IRB finds that a study is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), then it may waive consent, provided an appropriate mechanism for protecting the children is substituted, and provided further that the waiver is not inconsistent with federal, state or local law (i.e., the research cannot be FDA-regulated because FDA regulations do not provide for waiver of consent under these circumstances). The choice of an appropriate mechanism to protect the children participants depends on the nature and purpose of the proposed activities, the risk and anticipated benefit to the research participants, and their age, maturity, status and condition.

Under 45 CFR § 46.408(d), permission of parents or guardians for their children to participate in research must be documented by a signature on the consent/permission form, unless a waiver of consent/permission or documentation is approved by the IRB. The IRB will determine whether parental permission is required of both parents, of one parent, or if a waiver of parental permission or permission documentation is warranted, based on the criteria in the regulations and this policy as outlined above.

1.5.6 Children Assent Requirements

Under 45 CFR § 46.408(a), when, in the IRB’s judgment, children are capable of providing assent, the IRB must determine that adequate provisions are made for soliciting their assent. The IRB will additionally determine how assent will be solicited, obtained and documented. In determining whether children are capable of assenting, the IRB will take into account their ages, maturity, and psychological state. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. 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, then the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the participants are capable of assenting, the IRB still may waive the assent requirement in accord with 45 CFR § 46.116.

Under 45 CFR § 46.408(e), when the IRB determines that assent is required it shall also determine whether and how assent must be documented. Assent forms are designed similarly to consent forms and should include the purpose, procedures, risks and benefits of participating in a particular research study. The assent should be written at the age level of the children, with jargon and technical terms explained or removed.

For children aged seven and under, the IRB recommends that the Investigators verbally explain the study to the child, including its purpose, procedures, and potential risks and benefits (if appropriate, depending on the child’s age, maturity and development). For children aged seven through 17 years, the IRB typically requires written assent from the child, although this may be waived by the IRB. Depending on the study, its procedures, risk and benefits, the IRB may also approve verbal assent. Assent (written and verbal) should be obtained in the presence of a parent or legal guardian, unless the study procedures are taking place in a setting (such as a school) where parents are not usually present. However, in nearly all cases, a child’s assent must be accompanied by the permission or consent of the child’s parent or guardian.

1.5.7 Additional Requirements for Wards and Foster Children

Under 45 CFR § 46.409(a), children who are wards of the state or any other agency, institution, or entity can be included in research approved under § 46.406 or § 46.407 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.

Even if such research is approved under 45 CFR § 46.409(a), 45 CFR § 46.409(b) requires the appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall 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.

Massachusetts law (MGL Chapter 119, et. seq.) allows the Department of Children and Families to remove children from their parents’ custody in certain circumstances, but the placement of a child in foster care does not automatically terminate all parental rights. Because these situations are complicated, investigators who wish to enroll foster children in research are urged to consult in advance with the IRB.

### 1.5.8 Child Abuse Reporting

Research proposals involving children ordinarily must include a plan for reporting suspected abuse learned in the course of the research to the Massachusetts Department of Children and Families (DCF) and additionally include a statement in the consent and assent forms that suspected child abuse or neglect may be reported to DCF.

Certain people, as a function of their professions or provisions, are deemed to be mandated reporters. Under Massachusetts law, (MGL Chapter 119, § 51A), mandated reporters include any: “physician, medical intern, hospital personnel engaged in the examination, care or treatment of persons, medical examiner, psychologist, emergency medical technician, dentist, nurse, chiropractor, podiatrist, optometrist, osteopath, public or private school teacher, educational administrator, guidance or family counselor, day care worker or any person paid to care for or work with a child in any public or private facility, or home or program funded by the commonwealth or licensed pursuant to the provisions of chapter twenty-eight A, which provides day care or residential services to children or which provides the services of child care resource and referral agencies, voucher management agencies, family day care systems and child care food programs, probation officer, clerk/magistrate of the district courts, parole officer, social worker, foster parent, firefighter or policeman, licensor of the office of child care services or any successor agency, school attendance officer, allied mental health and human services professional as licensed pursuant to the provisions of section one hundred and sixty-five of chapter one hundred and twelve, drug and alcoholism counselor, psychiatrist, and clinical social worker, priest, rabbi, clergy member, ordained or licensed minister, leader of any church or religious body, accredited Christian Science practitioner, person performing official duties on behalf of a church or religious body that are recognized as the duties of a priest, rabbi, clergy, ordained or licensed minister, leader of any church or religious body, or accredited Christian Science practitioner, or person employed by a church or religious body to supervise, educate, coach, train or counsel a child on a regular basis.”

Reports must be made where the mandated reporter, in his or her professional capacity, has reasonable cause to believe that a child under the age of 18 is suffering physical or emotional injury resulting from abuse inflicted upon him or her which causes harm or substantial risk of harm to the child's health or welfare, including sexual abuse, or from neglect, including malnutrition, or who is determined to be physically dependent upon an addictive drug at birth. A mandated reporter must immediately make a verbal report to DCF and must make a written report within 48 hours.