Lifespan

Human Research Protection Program Policy and Procedure Manual

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ORA – RRC - 001

1.1 Mission:

Rhode Island Hospital, The Miriam Hospital, Emma Pendleton Bradley Hospital, Newport Hospital, and Gateway Healthcare are collectively known as “Lifespan” for the purposes of this manual. Other entities, may, from time to time, join Lifespan, and are included in this policy as appropriate. The purpose of the manual is to set forth policies and procedures regarding the conduct, administration and evaluation of the Lifespan Human Research Protection Program.

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

In order to fulfill this mission, Lifespan has established a human research protections program (HRPP). The mission of the HRPP is:

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

The HRPP is a multi-tiered program involving Executive Management, the Senior Vice President and Chief Research Officer, The Office of Research Administration (ORA), The Research Protection Office (RPO), the Institutional Review Boards (IRB), investigators and research support staff. Advisory groups include the Research Advisory Committee and the IRB Leadership Group. The HRPP includes mechanisms to:

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

1.2 Institutional Authority

The Lifespan Human Research Protection Program operates under the authority of the Lifespan Corporate Compliance Policy, "Lifespan Research Policy, CCPM 23". As stated in that policy, the operating procedures in this document serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the Lifespan. The Lifespan Corporate Policy and these operating procedures are made available to all Lifespan investigators and research staff and are posted on the ORA website: http://www.lifespan.org/research-administration-policies

1.3 Definitions

Human Participants Research – means any activity that meets the definition of "research" and involves "human subjects" as defined in either the Common Rule or FDA regulations.

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

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

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

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

- Private information as defined in 45 CFR§46.102(f) means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- Identifiable information as defined in 45 CFR§46.102(f) means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

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

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

An experiment, as defined in 21 CFR§312, includes any use of a drug other than the use of a marketed (approved) drug in the course of medical practice.

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

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

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

Research Under the Auspices of Lifespan. Research under the auspices of the institution includes research conducted at this institution, conducted by or under the direction of any employee or agent of this institution (including students) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, or involving the use of this institution's non-public information to identify or contact human subjects.

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

1.3.1Types of human subject research at Lifespan

Lifespan conducts many types of research, i.e., biomedical, social science and behavioral research. As per the definitions above all research engaged in at Lifespan that involves human participants is covered by the HRPP.

An activity is covered by the HRPP when:

- It is considered ***"human subject research"*** - as defined in any one of the following:
  - FDA regulations
  - DHHS regulations or other Common Rule regulations
  - Other federal agencies as they apply e.g., DoD sponsored studies.

and

- Lifespan (or its employees or agents) is ***engaged*** in the research – as defined by OHRP rules of engagement Engagement of Institutions in Human Subjects Research. http://www.hhs.gov/ohrp/policy/engage08.html

1.4 Ethical Principles

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

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

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.

The Lifespan Human Research Protection Program (HRPP), in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

1.5 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law and institutional policies. All human subjects research at Lifespan is conducted in accordance with the policy and regulations found in 45 CFR§46and 21 CFR§50 and 56,

and RI State regulations: Title 23, Health and Safety, Chapter 23-17, Licensing of Health Care Facilities, Section 23-17-19.1. and found at : **http://www.rilin.state.ri.us/Statutes/TITLE23/23-17/23-17-19.1.HTM**

The actions of Lifespan will also conform to all other applicable federal, state, and local laws and regulations.

1.6 Federalwide Assurance (FWA)

The HRPP operates under the authority of its current Federalwide Assurances (FWA00001230 Rhode Island Hospital; FWA00003538 The Miriam Hospital; FWA00001129 Emma Pendleton Bradley Hospital; FWA00003435 Newport Hospital; FWA 00022347 Gateway Health) and provides support to three registered Institutional Review Board panels (two at Rhode Island Hospital and one at The Miriam Hospital) which review all human research protocols.

1.7 Institutional Official

The ultimate responsibility of the HRPP resides with the Senior Vice President and Chief Research Officer, who serves as the Institutional Official (IO) of the program. The IO is responsible for ensuring Lifespan's HRPP has the resources and support necessary to comply with all institutional policies and with federal regulations and guidelines that govern human subject's research. The IO is legally authorized to represent Lifespan. The IO is the signatory of the FWA and assumes the obligations of the FWA. The IO is the point of contact for correspondence addressing human research with the DHHS Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA) and any other federal regulatory agencies.

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

1.8 Written policies and procedures

The Lifespan Policies and Procedures for Human Research Protection Program Manual detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the Lifespan IRB.

The policies and procedures manual is not a static document. The policies and procedures are reviewed and revised by the Director of the RPO, Administrative Director of the ORA, the Institutional Review Board, and Lifespan counsel, as necessary. The Senior Vice President and Chief Research Officer will approve all revisions of the policies and procedures.

The Administrative Director of the ORA will keep the Lifespan research community apprised of new information that may affect the human research protection program,

including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through campus electronic mailing lists. The policies and procedures will be available on the Lifespan IRB website and copies will be available upon request.

1.9 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects (HS) participating in research. It consists of various individuals and committees such as: Executive Management, the Senior Vice President and Chief Research Officer, the Administrative Director (AD) of the ORA, the Director of the RPO, the Manager of the RPO, the IRB, other committees or subcommittees addressing human subjects protection (e.g., Biohazards and Laboratory Safety Committee, Recombinant DNA Committee as applicable to HS, Radiation Safety, Conflict of Interest), investigators, IRB staff, research staff, and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

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

1.10 Senior Vice President and Chief Research Officer

As detailed above (*Institutional Official of the HRPP*), the ultimate responsibility of the HRPP resides with the Senior Vice President and Chief Research Officer of Research, who serves as the Institutional Official of the program. The responsibility for the HRPP at Lifespan may be delegated by the Institutional Official to the Administrative Director of the ORA.

1.10.1 Administrative Director of the ORA

The Administrative Director of the ORA reports to the Senior Vice President and Chief Research Officer and is responsible for:

1. Developing, managing and evaluating policies and procedures that ensure compliance with all state, and federal regulations governing research. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing all aspects of the HRPP program.
2. The supervision of the Director, Research Protection Office (Director, RPO). Efforts of the HRPP may be delegated to this administrator.
3. The supervisor of the Research Compliance Program Manager.
4. Advising the Senior Vice President and Chief Research Officer on key matters regarding research at Lifespan.
5. Implementing the institution’s HRPP policy.
6. Ensuring FWAs are submitted, approved, implemented and maintained through the Senior Vice President and Chief Research Officer and the Department of Health and Human Services Office of Human Research Protection (OHRP).

7. Managing the finances of the Lifespan HRPP.
8. Assisting investigators in their efforts to carry out Lifespan's research mission.
9. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
10. Developing training requirements as required and as appropriate for investigators, subcommittee members and research staff, and ensuring that training is completed on a timely basis.

1.10.2 Director, Research Protection Office

The Director of the RPO reports to the Administrative Director of the ORA and is responsible for:

1. Serving as the contact person to OHRP and FDA
2. Submitting and maintaining approved FWAs with DHSS
3. Serving as the regulatory resource to the research community on the use of human subjects
4. Providing support and training to investigators and IRB members
5. Orienting new IRB members
6. Developing policies and procedures that ensure compliance with all state, federal and institutional regulations governing research
7. Supervising the operations of the IRB committees
8. Overseeing the function of the Research Protection Office Committees

1.10.3 Institutional Review Board (IRB)

Lifespan maintains Institutional Review Boards (IRBs) to review research protocols involving human subjects. Lifespan has three registered Institutional Review Boards - RIH IRB #1, RIH IRB #2, and TMH IRB, appointed by the Senior Vice President and Chief Research Officer. The IRBs are established as Lifespan affiliate committees. As such, through IRB Authorization Agreements (IAA), the IRBs established at Rhode Island Hospital and The Miriam Hospital serves Newport Hospital, Gateway Healthcare and Emma Pendleton Bradley Hospital as well. Each affiliate has a distinct Federal Wide Assurance that designates one or more of the affiliate IRBs as a reviewing IRB. Under such an arrangement, those affiliates without an established IRB, agree through their IAA to abide by the research policies of the affiliate with the designated reviewing IRB.

Since the policies and procedures for all three IRBs are equivalent, they will be collectively referred to in this document as "the IRB" and the Chairs of the IRBs will be collectively referred to as "the Chair".

The IRBs are autonomous administrative bodies established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of Lifespan. The IRB has the following authority:

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

All IRB approved research studies are subject to ongoing review, which must be conducted, as per the federal regulations, at least once annually by the IRB. If approval by the IRB lapses, all research activity must stop unless the IRB finds that there is an over-riding safety concern or ethical issue involved such that it is in the best interests of the individual participants to continue participating in the research interventions or interactions.

The IRB has jurisdiction over all human subject research conducted under the auspices of the institution, regardless of funding source. Research under the auspices of the institution includes research conducted at this institution, conducted by or under the direction of any employee or agent of their institution (including students) in connection with his or her institutional responsibilities, conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, or involving the use of this institution's non-public information to identify or contact human subjects. No research involving human subjects may commence until it receives all the required approvals.

The IRB prospectively reviews and makes decisions concerning all human research conducted at its facilities or by its employees or agents, or under its auspices. The IRB is responsible for the protection of rights and welfare of human research subjects at the Lifespan. It discharges this duty by complying with the requirements of the Common Rule; state regulations, the FWA; and institutional policies. (See Section 2 for a detailed discussion of the IRB)

1.10.4 Lifespan Counsel's Office

The Lifespan HRPP relies on Lifespan Corporate Counsel for the interpretations and applications of Rhode Island law and the laws of any other jurisdiction where research is conducted as they apply to human subject's research.

1.10.5 The Investigator

The investigator is the ultimate protector on the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards and for developing a protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent and the investigator must establish and maintain an open line of communication with all

research subjects within his/her responsibility. In addition to complying will all the policies and standards of the governing regulatory bodies; the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff completes appropriate training and must obtain all required approvals prior to initiating research. When investigational drugs or devices are used, the investigator is responsible for having written procedures for their storage, security, dispensing and disposal. This accountability may be coordinated through the Research Pharmacist for drugs.

1.10.6 Relationship between Components

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

The IRB may, as appropriate, refer the protocol to the Radiation Safety Committee, the Biohazards and Laboratory Safety Committee and/or the Recombinant DNA Committee. Final approval of the IRB review will be held until all other applicable reviews have been conducted.

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

Protocol-specific coordination:

The Research Application, which must be submitted with every protocol, requires Principal Investigators (PIs) to indicate institutional support that may be required for the research, including, but not limited to:

- Laboratory
- Medicine
- Pharmacy
- Radiology
- Nuclear Medicine
- Nursing
- Psychiatry
- Outpatient
- Surgery
- Other

For any departments that are indicated, a letter of support or collaboration must be included with the signature of the Department Head. The protocol will be reviewed in the HRPP Office to ensure that all necessary letters are included.

1.10.7 HRPP Operations

In addition to the leadership structure described above, other members of the HRPP include the RPO Manager, full-time RPO Coordinators and RPO Assistants.

1.10.8 HRPP Office

The Lifespan HRPP Office, known to the research community as the Research Protection Office and used interchangeably in this document, as a unit of the Office of Research Administration, reports directly to the Senior Vice President and Chief Research Officer (who also serves as the Institutional Official and the Signatory Official on the Federal-wide Assurance) through the Administrative Director, ORA, and the Office is supervised by the Director of the Research Protection Office who is the primary contact at Lifespan for the Office for Human Research Protections, Department of Health and Human Services. These two officials work closely with the Chairs of the IRBs in the development of policy and procedures. The AD, through the Director of the Research Protection Offices, may delegate responsibilities.

The Director of the Research Protection Office has day-to-day responsibilities for the operation of the HRPP. This includes responding to Investigators', students', and staff questions about human subjects research as well as organizing and documenting the review process. Additionally, the office is staffed by a Manager, Coordinator(s) and Committee Assistant(s). The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis.

1.10.9 Manager, Research Protection Office

The Manager of the Research Protection Office supervises the staff of the Research Protection Office and is responsible for assisting the Director of the RPO in all aspects of the HRPP throughout the review process of a research proposal involving human subjects. This responsibility, through the coordinators, includes the initial review of documents and screening of research proposals prior to its review by the IRB, as well as serving as the liaison between the investigators and the IRB. The Manager of the RPO reviews the IRB for accuracy and ensures proper training, documentation of discussions including discussions and actions taken by IRB during convened meetings.

1.10.10 Research Protection Office Coordinator

The Research Protection Office Coordinators are responsible for reviewing all submissions to the IRB for accuracy and completeness. The coordinators provide support to the IRB chairs, the IRB members, and the Research Protection Office Director/Manager. The coordinators are responsible for communicating the IRBs requests to the investigators and ensuring appropriate responses are submitted. The Research Protection Office Coordinator is also responsible for IRB record retention. The Research Protection Office Coordinator is responsible for maintaining complete IRB

files and records of all research protocols, IRB correspondence (including e-mails) as well as Research Credentialing file records of investigators and research staff (all records are maintained in the eIRB system).

1.10.11 Research Protection Office Assistants

The Research Protection Office Assistants field phone calls, process all submitted materials, maintain the research eIRB system, prepare and forward all committee action letters, communicate with research staff regarding required documents for revisions, continuing reviews, expedited studies and requests of the coordinators or IRB chair and prepare meeting agendas.

1.10.12 Selection, Supervision and Evaluation of HRPP Supporting Staff

Selection Process:

Vacant and new positions are posted throughout the Lifespan system as well as advertised in newspaper ads and through online postings. Applicants are screened by a Human Resources Recruiter and appropriate applicants are then referred to the Director for interviews and selection.

Supervision:

Coordinators and Committee Assistants are directly supervised by the Manager.

Evaluation:

All staff are continuously evaluated, but no less than annually through a standardized system-wide process.

1.11 HRPP Resources

The HRPP Office, is located in Coro West, Suite 1.300 and has adequate office space, meeting space, storage space and equipment to perform the functions required for the HRPP. The adequacy of personnel and non-personnel resources of the HRPP program is assessed on an annual basis by the AD and Director with the HRPP staff and are reviewed and approved by the IO.

The Lifespan Institutional Official (Senior Vice President and Chief Research Officer) provides resources to the IRB and HRPP Office, including an eIRB system, adequate meeting and office space, and staff for conducting IRB business. Office equipment and supplies, including technical support, file cabinets, computers, internet access, and copy machines, are available to the IRB and staff. The resources provided for the IRB and HRPP Office are reviewed during the annual budget review process.

1.12 Conduct of QA/QI Activities for IRB Operation

The overall objective of Lifespan's HRPP Quality Assurance / Quality Improvement Plan is to achieve and maintain compliance with organizational policies and procedures and applicable federal, state, and local laws. The Quality Assurance/Quality Improvement Plan is comprised of (1) the HRPP Institutional Audits and Compliance Reviews

(1.12.1); (2) IRB Internal Compliance Reviews (1.12.4); and, (3) the HRPP Internal Quality Review and Improvement (1.12.5). Each of the three parts of the QA/QI has measurable objectives as described below.

The Quality Assurance / Quality Improvement Plans are managed and implemented by the Research Compliance Program Manager, (or others so delegated by the AD, ORA) reporting directly to the Administrative Director of the ORA. All records undertaken to assess the HRPP program quality, efficiency, and effectiveness will be documented in writing, and retained by the Research Compliance Program Manager for at least six (6) years. All results from QA/QI activities will be reviewed with the IO.

1.12.1 Institutional Audits and Compliance Reviews

Lifespan's HRPP Compliance Reviews consist of audits and periodic compliance reviews conducted to assess investigator compliance with federal, state, and local law, and Lifespan policies, and to identify areas for improvement, and suggest recommendations based on existing policies and procedures. Lifespan conducts the following types of audits: (1) "For Cause Audits" which are directed audits of IRB-approved research studies are in response to identified concerns; (2) periodic directed "not for cause" compliance reviews which are conducted using a systematic method to review IRB-approved research; and (3) self-assessments and follow up reviews on a regular basis.

Lifespan's HRPP Compliance Review Program is committed to completing "for cause audits" as necessary and at least 3 directed "not for cause" audits and at least 30 "self-assessments" annually.

The results will be reported to the Principal Investigator, the Director of the Research Protection Office, the Administrative Director, and the IRB Chair (s). Quarterly summaries of compliance reviews will be reported to the IRB(s) and the IO.

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

a) Requesting progress reports from researchers;
b) Examining investigator-held research records;
c) Observing research sites where research involving human research subjects and/or the informed consent process is being conducted;
d) Auditing advertisements and other recruiting materials as deemed appropriate by the IRB;
e) Reviewing projects to verify from sources other than the researcher that no unapproved changes have occurred since previous review;
f) Monitoring conflict of interest concerns to assure the consent documents include the appropriate information and disclosures;
g) Monitoring HIPAA authorizations (i.e. Waiver of Authorization and Preparatory to Research);
h) Conducting other monitoring or auditing activities as deemed appropriate by the IRBs;

i) In rare cases, if applicable, contact research subjects.

1.12.2 External Site Audits and Compliance Reviews

Directed audits and compliance reviews may be conducted at external sites, where Lifespan's IRB serves as the "IRB of Record," to assess compliance with federal, state, and local law, research subject safety, and IRB policies and procedures. These directed audits are implemented in response to identified concerns that require an IRB determination. These reviews may include items listed in section 1.12.1 above.

1.12.3 Reporting and Disposition

The results of all IRB audits are reported to the Principal Investigator, the Director, Research Protection Office, the Administrative Director, and the IRB Chair(s). Any noncompliance will be handled according the procedures in Section 11.

If an audit or review finds that subjects in a research project have been exposed to unexpected serious harm, the incumbent will promptly report such findings to the Director, Research Protection Office, the Administrative Director and the IRB Chair(s).

Additionally, the Research Compliance Program Manager will report quarterly to the fully convened Lifespan IRBs. The report will consist of updates of ongoing audits and self-assessments. The Research Compliance Program Manager will report on trends resulting from the self-assessments and other compliance activity.

1.12.4 IRB Internal Compliance Reviews

The purpose of IRB Internal Compliance Reviews is to determine adherence to the federal, state and local regulations regarding the review of human subject protocols. The results may impact current practices and may require additional educational activities, and will be reported to the Administrative Director and IO.

The Research Compliance Program Manager will, at least quarterly, select a full board meeting of one IRB and:

1. Review of the IRB minutes to determine that adequate documentation of the meeting discussion has occurred. This review will include assessing the documentation surrounding the discussion for protections of vulnerable populations as well as other risk/benefit ratio and consent issues that are included in the criteria for approval. The Compliance Program Manager will verify that the minutes include a statement that substantive modifications and clarifications requested by the IRB will be returned for full board review by the convened board. The minutes of the IRB meetings will be monitored to confirmed that formal suspension/termination actions were performed according to IRB policies and documented as such in the minutes;
2. Assess the IRB minutes to assure that quorum was met and maintained;
3. Assess the current adverse event reporting process;

4. Assess that privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented in the IRB minutes;
5. Evaluate the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
6. Observe IRB meetings or other related activities;
7. Review eIRB files to assure appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
8. Review of protocol evaluations by the IRB members;
9. Verification of IRB approvals for collaborating institutions or external performance sites;
10. This quarterly review will also include projects involving vulnerable subjects that received expedited review on the chosen agenda. The Manager will verify that the expedited reviewer has completed the reviewer worksheet to document protocol-specific determinations that the criteria for including vulnerable populations have been met, and that this documentation has been maintained in the study file;
11. Other monitoring or auditing activities deemed appropriate by the IRB.

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

1.12.5 HRPP Internal Quality Review and Improvement

The third aspect of the Lifespan QA/QI program focuses on the quality improvement aspect of the program. The purpose of this review is to determine how the HRPP program is working and where improvements may be made.

A. The IO, AD of ORA, and the Director of the RPO will evaluate the IRB Chairs. The combined results may be reviewed by the IO, who may meet annually with the Chairs to discuss their performance and to solicit feedback for program improvement.

B. IRB Chairs, members, and alternates who attended meetings during the evaluation period may complete an evaluation checklist once a year, which includes a self-evaluation section on their own performance. The content areas on this “IRB Self-Assessment” include:

- Conduct of the IRB meetings
- Administrative Support
- Chairperson
- Committee Members
- Meeting Environment
- Institutional Support

- Other Suggestions

The complete surveys will be reviewed by the IO, AD of ORA, and the Director of the Research Protection Office. Results, issues, and trends will be shared with the HRPP Staff, IRB Chair(s), members and others as applicable.

C. Metrics, as prescribed by the Association for the Accreditation of Human Research Protect ion Program (AAHRPP), will be tracked, assessed, and reported yearly. The following metrics will be measured (if available):

- Number of active protocols (exempt, expedited, full board)
- Number of FTEs dedicated to the IRB and HRPP function
- Cost of the HRPP program
- Numbers of investigators and their research staff
- Mean number of days from submission to review and approval for new studies for full board and expedited submissions
- Mean number of days from submission to exempt determination
- Percentage of protocols disapproved by the IRB
- Number of protocol deviations
- Number of complaints from research participants received
- Number of cases of alleged non-compliance investigated
- Number of determinations of continuing non-compliance
- Number of unanticipated problems investigated
- Number of unanticipated problems involving risks to participants or others
- Number of “for cause” audits of investigator protocols
- Number of random audits of investigator protocols
- Number of “for cause” audits of IRB records conducted
- Number of random audits of IRB records conducted
- Number of FDA inspections of investigators or the IRB(s)

Metrics will be used to assess the overall HRPP program to determine if the resources needed to implement the program and provide continuing education to investigators, research staff, and IRB members are adequate.

The Administrative Director ORA will complete Table 2 of the AAHRPP “Annual Report Form”. This table allows for a comparison of performance on specific elements of the HRPP program between the current and previous year. Changes are quantified as gradations of improvement, no change, and worsening.

The Administrative Director and the Director of the Research Protections Program will use the annual “Metrics on Human Research Protection Program Performance” released by AAHRPP to benchmark performance in the coming year.

The aggregate results of these assessments, as reported to the IO, will be used to evaluate current practices, establish whether additional education activities are needed, and if resources are adequate.

1.13 Collaborative Research Projects

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

It is the policy of Lifespan to assure that all facilities participating in a human subjects study receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRBs of record for each participating facility and, where appropriate, the IRB of record for the coordinating facility.

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

- When Lifespan relies on another IRB, the Director/Manager of the RPO office will ensure that Lifespan standards are being met. If the other IRB is part of an accredited HRPP, then it will be assumed that the Lifespan standards are being met. If the other IRB is not part of an accredited HRPP, then the RPO Director/Manager will review the policies and procedures of the IRB to determine whether it meets Lifespan standards. Lifespan IRB is required to verify compliance with use of template consent forms, and local research context by review of the following: local training credentials, institutional policies (e.g. HIPAA, COI), state and local laws, and local population.

If Lifespan is the coordinating facility the Principal Investigator must document how the important human subject protection information will be communicated to the other participating facilities engaged in the research study. The investigator is responsible for serving as the single liaison with outside regulatory agencies, with other participating facilities, and for all aspects of internal review and oversight procedures. The investigator is responsible for ensuring that all participating facilities obtain review and approval from their IRB of record and adopt all protocol modifications in a timely fashion. The investigator is responsible for ensuring that the research study is reviewed

and approved by any other appropriate committees at the coordinating facility and at the participating facilities prior to enrollment of participants.

2 Institutional Review Board

2.1 Policy Statement

All Lifespan affiliated IRBs are guided by the ethical principles as set forth in the Belmont Report and apply Department of Health and Human Services (DHHS) regulations (45 CFR§46, including Subparts A, B, C, & D) to all proposed research involving human subjects, regardless of sponsorship. Additional regulations such as the U.S. Food and Drug Administration Human Subjects Regulations (21 CFR§§50, 56, 312 & 812), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Good Clinical Practice, International Conference on Harmonization (ICH) as they relate to DHHS and FDA regulations and applicable Rhode Island State laws and regulations are also applied.

The mission of the Lifespan affiliated IRBs is to protect the rights and welfare of human research subjects recruited to participate in research activities conducted by Lifespan Investigators through ethically responsible and scientifically valid research, continuous education of the research community, monitoring of research activities, and compliance with the federal regulations and institutional policies and procedures.

The IRB Committees are required to have varying backgrounds and expertise to provide complete and thorough review of research activities commonly conducted by the Institution.

The following describes the authority, role and procedures of the Lifespan Institutional Review Board (IRB).

2.2 IRB Authority

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

1. To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted under the auspices of Lifespan;
2. To suspend or terminate approval of research not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to participants;
3. To observe, or have a third party observe, the consent process; and
4. To observe, or have a third party observe, the conduct of the research.
5. Determine whether an investigational device is a significant risk device and if so require that an Investigational Device Exemption (IDE) or waiver by the FDA will be obtained prior to the IRB approval of the project involving the device, if applicable. Such determination will be made at a convened meeting of the IRB. The IRB shall consider the significant risk device as defined in CFR 812.3(m).
6. Conduct continuing review at intervals appropriate to the degree of risk but not less than once per year.
7. Submit certification of its review and approval for all funded research involving human subjects in accordance with the regulations of the sponsor.

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

2.3 Number of IRBs

There are currently three registered Institutional Review Boards - RIH IRB #1, RIH IRB #2, and TMH IRB. As noted in Section 1.10.3, for the purposes of this document, all three IRBs will be referred to collectively as "the IRB". The Institutional Official, the Administrative Director of the ORA, the Director, Research Protection Office, and the Chairs of the IRBs will review the activity of the IRB and make a determination as to the appropriate number of IRBs that are needed for the institution.

2.4 Roles and Responsibilities

2.4.1 Chairperson of the IRB

The Lifespan Institutional Official in consultation and approval with the IRB members, and the Administrative Director of the ORA, appoints a Chair and Associate Chair(s) for each of the IRBs to serve for renewable terms. Any change in appointment, including reappointment or removal, requires written notification.

As noted in Section 1.10.3, for the purposes of this document, the Chairs will be collectively referred to as "the Chair".

The Chair should play a leadership role in establishing and implementing IRB policy. As a primary representative of IRB decisions, the IRB Chair should have shared authority over all IRB policy and procedures in collaboration with the institutional official and/or the ORA Administrative Director and the RPO Director. The responsibilities of the IRB Chair include but may not be limited to the following:

- The Chair should represent the IRB in discussions with other segments of the organization.
- The Chair should represent the organization in discussions with federal authorities.
- The Chair should direct the proceedings and discussion of the full-committee meeting. This includes keeping the discussion focused on important IRB issues and seeing that the full-committee meeting process is both efficient and effective.
- The IRB Chairs will vote on protocols at the full-committee meeting.
- The Chair should have an in-depth understanding of the ethical issues, state law, institutional policy, and federal research regulations that are applicable to studies that are reviewed by the IRB. The IRB Chair is not expected to be the only, or

ultimate, authority on compliance issues. The IO, Administrative Director, and the Director and Manager of the Research Protection Office, also take responsibility for compliance verification, but the IRB Chair is expected to be an active and knowledgeable partner in this aspect of the IRB system.

- The Chair or designee should assist IRB administration in the drafting of letters from the IRB to researchers regarding IRB decisions.
- The Chair should review and sign or designate signature authority for IRB response letters in a timely fashion.
- The Chair or designee should review and make decisions about responses to conditions for IRB approval of research in a timely fashion.
- The Chair should serve as the reviewer for research that is reviewed by an expedited process. This task is often shared with other members of the IRB, depending on expertise.
- The Chair should represent the IRB in defending or discussing IRB decisions with researchers.

The chairs or designees have the authority to immediately suspend an investigator or study if a complaint or concern warrants immediate action. The full IRB will be informed of this action as soon as possible.

The performance of IRB Chair will be reviewed by the Administrative Director of the ORA Office in consultation with the Director of the Research Protection Office, and the Institutional Official. If the Chair is not acting in accordance with the IRB's mission, following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she will be removed by the IO.

2.4.2 Associate Chair of the IRB

The Associate Chair serves as the Chair of the IRB in the absence of the Chair and has the same qualifications, authority, and duties as Chair. The performance of the IRB Associate Chair may be reviewed on an annual basis by the Administrative Director of the ORA in consultation with the Director of the Research Protection Office, and the Institutional Official.

2.4.3 Subcommittees of the IRB

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

2.5 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, specific community concerns in addition to

representation by multiple, diverse professions, knowledge and experience with vulnerable subjects, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at Lifespan. Lifespan has procedures (See Section 3) that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

In addition, the IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participates in Lifespan research.

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

2.6 Composition of the IRB

1. The IRB will have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.
2. The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.
3. In addition to possessing the professional competence necessary to review specific research activities, The IRB will be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
4. If the IRB regularly reviews research that involves a vulnerable category of subjects (e.g., children, prisoners, pregnant women, or handicapped or mentally disabled persons), consideration will be given to the inclusion of one or more individuals on the IRB, who are knowledgeable about and experienced in working with these subjects. When protocols involve vulnerable populations, the review process may include one or more individuals who are knowledgeable about or experienced in working with these participants, either as members of the IRB or as consultants (see Section 2.10).
5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. The IRB shall not consist entirely of members of one profession.

6. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
7. The IRB includes at least one member who is not otherwise affiliated with institution and who is not part of the immediate family of a person who is affiliated with the institution and who represents the perspective of research subjects.
8. One member may satisfy more than one membership category.
9. The administrators of Lifespan's HRPP RPO may be voting members of the IRB.

2.7 Appointment of Members to the IRB

The Senior Vice President and Chief Research Officer will solicit from the hospital President, department chiefs, or Administrative Director of the Office of Research Administration, candidates for membership on the IRB. Notification of selection will be sent from the Office of Research Administration to the perspective member. Appointment of the Chair and Associate Chair(s) will be by the Senior Vice President and Chief Research Officer. A hospital administrator may be an ex officio member and serve as the secretary of the IRB.

Appointments are made, on average, for a renewable three-year period of service. Any change in appointment, including reappointment or removal, requires written notification. Members may resign by written notification to the Chair.

The IRB Chair, the Director and Manager of the Research Protection Office, and the Administrative Director of the ORA will review the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

2.8 Alternate members

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

The IRB roster identifies the primary member(s) for whom each alternate member may substitute. The alternate member will not be counted as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

2.9 IRB Member Conflicts of Interest

IRB members and consultants will not participate in any IRB action taken, including the initial and continuing review of any project, in which the member has a conflict of interest, except to provide information requested by the IRB. IRB members are expected to self-identify conflicts of interest. A primary reviewer or expedited reviewer with a conflict of interest must notify the IRB staff who will re-assign the protocol.

An IRB member is considered to have a conflict of interest when the IRB member or an immediate family member (defined as spouse, domestic partner, dependent children, siblings, parents, or equivalents by marriage, or other individuals residing in the household) of the IRB member:

1. Where the member is listed as an investigator or participating in the research.
2. Where any investigator must report to or is under the supervision of a committee member
3. Has a significant financial interest related to the research as defined in Section 14.2
4. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a protocol

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

If the Conflict of Interest status of an IRB member changes during the course of a study, the IRB member is required to declare this to the IRB Chair, Director, Manager or Coordinator of the Research Protection Office.

2.10 Use of Consultants (Outside Reviewers)

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

Consultants will confirm they do not have a conflict of interest prior to review. Individuals who have a conflict of interest or whose spouse or family members have a conflict of interest with the sponsor of the research will not be invited to provide consultation.

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

Consultant documentation will be maintained in the eIRB system. Key information provided by consultants at meetings will be documented in the minutes.

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is

in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

2.10.1 IRB Member Responsibilities

IRB members have an understanding of basic ethical principles, the regulatory requirements, and the mechanics of serving on the IRB. The responsibilities of the IRB members include but may not be limited to the following:

- IRB members conduct prospective and continuing review of proposed research activities according to DHHS regulations 45 CFR§46, FDA regulations 21 CFR§§50 and 56 and when applicable, Federal, State and local laws, and institutional policies and procedures including the IRB.
- IRB members may evaluate the research proposal which may include consideration of research design, statistical power, equitable subject selection process, scientific and scholarly design etc.
- IRB members identify any conflicts of interest prior to the review of research activities and bring this to the attention of the IRB Support Staff for reassignment of the protocol. Members will complete conflict of interest statements at the beginning of each meeting. IRB members obtain guidance or additional information in order to conduct an adequate study evaluation. This may include the request of an additional reviewer or consultant with expertise in the area of research under review (e.g., a psychiatric consultant may be asked to review a study that requires a “wash-out” period followed by intervention with investigational or novel agents in a population that has a high likelihood of enrollment of subjects that are or may become cognitively impaired).
- IRB members are expected to be certified in human subject’s protection before they can become a primary reviewer for IRB actions and are expected to re-certify every three years.

2.11 Attendance Requirements

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

If an IRB member is to be absent for an extended period of time, such as for a sabbatical, he or she must notify the IRB at least 30 days in advance so that an appropriate replacement can be obtained. The replacement can be temporary, for the period of absence, or permanent if the member is not returning to the IRB. If the member has a designated alternate (See Section 2.8), the alternate can serve during the primary member’s absence, provided the IRB has been notified in advance. Members are expected to attend 8 out of 12 meetings on an annual basis.

2.12 Training / Ongoing Education- Chair, IRB and Staff in Regulations, Procedures

A vital component of a comprehensive human research protection program is an education program for the IRB Chair and the IRB members. Lifespan is committed to providing training and an on-going educational process for IRB members and the staff of the Research Protection Office related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

2.12.1 Orientation

All IRB members receive an orientation to the review of research involving human subjects with the Director or Manager of the RPO. This orientation includes a review of their responsibilities as members of the IRB. They are given a copy of "Institutional Review Board Member Handbook" by Robert Amdur, MD and access toThe Lifespan HRPP Policy and Procedure manual which is located in the eIRB system in the forms library. A review is included of the IRB application forms and process as well as the Federal and State regulations governing human subject's research. In addition, all members are given training on the use of Lifespan's eIRB system.

2.12.2 Initial Education

IRB members are required to be certified in the basic human subject's protection educational program to become primary reviewers. They are instructed to access the CITI on-line program for IRB members.

2.12.3 Continuing Education

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

- In-service training at IRB meetings;
- Copies of appropriate publications;
- Identification and dissemination by the Director of the RPO, the Administrative Director of the ORA, and the IRB Chair(s) of new information that might have affected the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members via email, mail, or during IRB meetings;
- Access to the eIRB system library resources.

2.12.4 IRB Professional Staff:

IRB staff is also required to certify in human subject protection and re-certify every three years using the CITI on-line program. The coordinators are given the opportunity to attend national meetings such as PRIM&R, regional meetings hosted by regional institutions, and participate in webinars. Memberships in professional organizations are provided by the institution. Professional staff is encouraged to seek certification in their areas of expertise, such as Certified IRB Professional and Certified IRB Manager.

Subscriptions to Guide to Good Clinical Practices and Human Research Reports are provided for the staff as resources as well as the "IRB" periodical.

2.13 Liability Coverage for IRB Members

Lifespan's insurance coverage applies to employees and any other person authorized to act on behalf of Lifespan; or acts or omissions within the scope of their employment or authorized activity.

2.14 Review of IRB Member Performance

The IRB Members' performance will be reviewed by the Director of the Research Protection Office, the Administrative Director and the IRB Chair(s). The chairs may conduct a one on one evaluation of each IRB member annually either by phone, face to face or by letter/email. Specific criteria may be evaluated such as attendance, quality of review, timeliness of review, contribution to meetings, knowledge of regulations and institutional policies, communication with IRB staff, members, researchers, etc. Members who are not acting in accordance with the IRB's mission or policies and procedures or who have an undue number of absences will meet with the chair to discuss attendance or issues noted. The chair may decide to put the member on a probationary period or remove them from the IRB."

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2.15 Reporting and Investigation of Allegations of Undue Influence

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

To maintain the privacy of our IRB members and minimize the potential for coercion Lifespan maintains the privacy and confidentiality of its IRB members. Anyone outside the institution requesting rosters of the IRB members, except for Regulatory officials, will be forwarded anonymous listings of the member's specialty, scientific/non-scientific designation, and affiliation.

3 IRB Review Process

3.1 Policy Statement

All research involving humans that falls under the jurisdiction of the IRB for review and approval must meet the criteria for one of the following methods for review:

1. Exempt from IRB Committee Review
2. Expedited Review
3. Full Committee Review

Continuing review is necessary to determine whether the risk/benefit ratio has changed, whether there are unanticipated findings involving risks to participants, and whether any new information regarding the risks and benefits should be provided to participants. The IRB will determine that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of the rights and welfare of research participants. For multi-site trials continuing IRB review is required as long as participants are enrolled. This remains the case even after a protocol has been closed to enrolment at all sites and protocol-related intervention has been completed for all participants, even if research is limited to final data analysis.

Lifespan, in accordance with all applicable Federal regulations will at all convened IRB meeting have a quorum of members that includes a non-scientist, a scientist, as well as members who are diverse and sufficiently qualified through experience and expertise.

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

3.2 Definitions

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

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

1. the level of risks to subjects
2. the research design or methodology (adding procedures that are not eligible for expedited review [See Section 3.5] would not be considered a minor change)
3. the number of subjects enrolled in the research, i.e., an increase of greater than 10% in the number of subjects would not be considered a minor change if it increased risk.
4. the qualifications of the research team
5. the facilities available to support safe conduct of the research
6. any other factor which would warrant review of the proposed changes by the convened IRB.

Quorum. A quorum of the IRB consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. The non-scientist's attendance is required as part of quorum. The unaffiliated member, the member representing the perspective of research participants, and the non-scientific member may be the same person, or they may be represented by two or three different persons. At least one of the members representing the general perspective of research participants will be present at a minimum of 10 out of 12 meetings/year. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

Suspension of IRB approval: A suspension is a directive of the convened IRB or other authorized individual (See Section 3.10) to temporarily stop some or all previously approved research activities short. Suspended protocols remain open and require continuing review. A lapse of approval due to a lack of continuing review is not considered a suspension for these procedures.

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

3.3 Human Subjects Research Determination

The responsibility for initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of "human subject" and "research" in Section 1.3. Other activities may be defined as:

- Case reports, such activities are generally not systematic investigations, (see Section 17.5 for more information).
- Disease outbreak investigations, which are investigations into acute or chronic infectious diseases, conditions, or environmental hazards, and activities explicitly required by statute– when these activities are designed to identify and resolve a public health problem, and are not designed to contribute to generalizable knowledge, then review by the HRPP is not required.
- Quality improvement projects - When such activities are designed to monitor and verify ongoing program operations, review by the HRPP is not required.

  If the results of quality improvement are designed to be generalizable, then HRPP review is required (see "When should a QA study or a QI/QA project be submitted to the IRB for Review" in the eIRB system library of forms). Program evaluation and surveillance activities may or may not constitute human subjects research and should be determined by the investigator.

Since Lifespan will hold them responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the Research Protection Office. The request must be

made through a submission in the eIRB system. All requests must include sufficient documentation of the activity to support the determination.

Determinations as to whether an activity constitutes human subjects research will be made according to the definitions in Section 1.3 using a human subject's research checklist. Determinations regarding activities that are either clearly or clearly not human subject's research may be made by the Research Protection Office Director or designee. Determinations regarding less clear-cut activities will be referred to the IRB Chair or designee, who may make the determination or refer the matter to the full IRB.

Documentation of all determinations made through the Research Protection Office will be recorded and maintained in the Research Protection Office e-IRB system. Submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file in the e-IRB system.

The investigator in consultation with the IRB Chair or Director will determine if the research involving coded information or specimens constitutes human subjects research (according to the criteria in Section 17.4). When the investigator submits a formal submission, the request must include sufficient documentation of the activity to support the determination. Formal submissions will be responded to in writing and a copy of the submitted materials and determination letter/email will be kept on file in the e-IRB system.

3.4 Exempt Studies, 45 CFR 46 101

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

Reviewers will use the Exempt Reviewer Form to determine and document whether the protocol meets the exemption criteria.

3.4.1 Limitations on Research Subjects:

Vulnerable Populations:

1. Children: Exemption for research involving survey or interview procedures or observations of public behavior does NOT apply, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.
2. Prisoners: exemptions do NOT apply. Full Board IRB review may be required.

3.4.2 Categories of Exempt Research

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

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:
    a. research on regular and special education instructional strategies; or,
    b. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
    a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and,
    b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (2), if:
    a. the human subjects are elected or appointed public officials or candidates for public office; or
    b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. NOTE: In order to be eligible for this exemption, all of the materials have to exist at the time the research is proposed.
5. Research and demonstration projects which are conducted by or subject to the approval of federal Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs.
    e. Such projects must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements for IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the funding agency.
6. Taste and food quality evaluation and consumer acceptance studies,
    a. If wholesome foods without additives are consumed; or
    b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug

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

3.4.3 FDA Exemptions

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

1. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR§56.104(d)]

3.4.4 Additional Protections

Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report or the Health Information Portability and Accountability Act (HIPAA). The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

3.4.5 Exemption Request Procedures

The Principal Investigator must complete a full application to insure the IRB reviewer has complete information to determine the review status. The full application is kept on file in case the investigator submits a revision to protocol that takes it out of the exempt status. Should that happen, the investigator would have to submit a revision and requested documents for review.

Only the Chair of the IRB or designee, can determine the exempt status of a research proposal. Reviewers will use the Reviewer Form to determine and document whether the protocol meets the exemption criteria.

Research determined to be exempt from IRB review will be exempt from continuing review unless changes made to the protocol remove it from the exempt category and places it into an expedited or full review category.

A letter confirming the exempt status of the research will be issued to the investigator once all revisions are received in the ORA.

A Continuing Review Report is not required, however, the Exempt letter informs the PI that changes to the study that may change the determination must be submitted to the IRB as well personnel changes. The Office of Research Administration may periodically email the principal investigator, an Exempt Research Project status survey.

3.5 Expedited Review, 45 CFR§46.110

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

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

3.5.1 Categories of Research Eligible for Expedited Review

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

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

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.

The expedited review procedure may not be used for classified research involving human subjects. (Classified Research is Research, knowledge of the procedures and results of which, is restricted to individuals with United States government security clearances).

The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review-expedited or convened-utilized by the IRB.

Research Categories one (1) through seven (7) pertain to both initial and continuing IRB review:

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR§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§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. [Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."][45 CFR§46.402(a)]

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

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject’s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b) (4). This listing refers only to research that is not exempt.]

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR§46.101(b) (2) and (b) (3). This listing refers only to research that is not exempt.]

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new 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.

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

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

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

[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The

determination that "no additional risks have been identified" does not need to be made by the convened IRB.]

3.5.2 Expedited Review Procedures

Under an expedited review procedure, the review may be carried out by the IRB Chair or by one or more reviewers designated by the Chair from among members of the IRB. IRB members who serve as designees to the IRB Chair for expedited review will be matched as closely as possible with their field of expertise to the study.

The Chair will designate a list of IRB members eligible to conduct expedited review. The designees must be experienced voting members of the IRB. (There are several ways a member may achieve sufficient experience, including attendance at IRB meetings, targeted education, working with a mentor, independent study, and previous IRB service). The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. IRB members with a conflict of interest in the research (see Section 2.9 will not be selected).

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will review the same documentation that would normally be reviewed by a primary reviewer for a full-board review (See Section 3.6.5). The reviewer(s) conducting initial review complete the appropriate “Lifespan IRB Reviewer form” to determine whether the research meets the criteria allowing review using the expedited procedure and if so, whether the research meets the regulatory criteria for approval. If the research does not meet the criteria for expedited review, then the reviewer will indicate that the research requires full review by the IRB and the protocol will be placed on the next agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 3.7, 3.8 & 3.9 and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. If a reviewer cannot approve the research, they will check the Refer to Full Board checkbox on the Reviewer Form or select refer to full board in the eIRB system.

Reviewers will indicate approval, required modifications or deferral to the full board on the Lifespan IRB Reviewer worksheet and upload it to the eIRB system. If modifications are required the Research Protection Office staff will inform the investigator by e-mail. The IRB member will be notified when requested revisions or modifications/information has been provided for further review.

In the event that expedited review is carried out by more than one IRB member and the expedited reviewers disagree, the IRB Chair may make a final determination. Upon the discretion of the IRB Chair the protocol will be submitted to the convened IRB for review.

3.5.3 Informing the IRB

All members of the IRB will be apprised of all expedited reviews by means of a list in the agenda for the next scheduled meeting. Any IRB member can request to review the full protocol by contacting the Research Protection Office.

3.6 Convened IRB Meetings

Except when an expedited review procedure is used, the IRB will conduct initial and continuing reviews of all research at convened meetings at which a quorum (see 3.6.6) of the members is present.

3.6.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (usually once per month). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings can be found on the eIRB system.

Special emergency meetings may be called at any time by the Chair or the Director if deemed necessary.

3.6.2 Preliminary Review

The IRB Coordinators will perform a preliminary review of all protocol materials submitted to the Research Protection Office for determination of completeness and accuracy using the coordinator checklist. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed either by e-mail, phone or in person of missing materials and the necessary date of receipt for inclusion on that month's agenda.

In the case of a PI who is submitting a protocol for the first time or an investigator who may not be well-versed in the protocol submission procedures, individualized IRB consultations can be arranged. Specific questions about the IRB policies and procedures, determination of whether a particular protocol is human research, and what particular forms are required for a particular study may be submitted in writing to the IRB Coordinators or Director for information and/or clarification. Open training sessions for IRB submission are held twice a month in the Research Protection Office conference room. Individual appointments with the IRB Coordinators or Director can also be arranged and are strongly recommended for first-time submissions.

3.6.3 Primary Reviewers

After it has been determined that the protocol submission is complete, the IRB Coordinators, with the assistance of the RPO Director or Manager, will assign protocols for review paying close attention to the scientific content of the protocol and the potential reviewer's area of expertise. Two reviewers will be assigned to each new and full board revisions to protocol and a reviewer may be assigned several protocols or other research items for review. Reviewers are assigned to all protocols requiring initial review, continuing review, and modifications. When the IRB is presented with a

protocol which may be outside of the knowledge base of any of the IRB members, an outside consultant will be sought. (See item 2.10)

The primary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research,
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing IRB reviewer form and comments in eIRB system.

The primary reviewers will be notified of the availability of the application for review no later than 5 days prior to the convened meeting. The reviewer is encouraged to contact the coordinator and/or RPO Director or Manager prior to the convened IRB meeting to discuss issues regarding the research proposal.

If the primary reviewer notifies the Coordinator in advance of the meeting that they will be absent from the meeting or has a COI, a new reviewer may be assigned and materials will be provided. The new reviewer will be expected to review the materials prior to the meeting. Additionally, an absent reviewer can submit their written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary reviewer. It should be noted that all of the IRB members receive and are expected to review the entire package as described in section 3.6.5 for all studies, not just the ones they are responsible for reviewing for initial, continuing and review of modifications to approved research.

3.6.4 Pre-Meeting Distribution of Documents

All required materials need to be submitted in full 10 business days prior to the convened meeting for inclusion on the following IRB agenda. Deadline dates are published on the eIRB system. The meeting agenda will be prepared by the IRB coordinator, under the supervision of the RPO Director or Manager, and shared with the IRB members prior to the meeting. All IRB members are shared review materials which include the IRB agenda, prior month's meeting Minutes, applicable business items, and protocol review materials, no later than 5 business days before the scheduled meeting to allow sufficient time for the review process. Additionally, continuing education items may be provided at the meeting.

3.6.5 Materials received by the IRB

Each IRB member reviews the following documentation in eIRB system as applicable:

1. Complete Protocol and
2. Application form(s)
3. Proposed Consent / Parental Permission / Assent Form(s)
4. Recruitment materials / subject information

5. The investigator's current curriculum vitae or other documentation evidencing qualifications
6. Any other pertinent material

Two primary reviewers will review, as applicable: any relevant data collection instruments (including all surveys and questionnaires), grant applications; the sponsor's protocol; the investigator's brochure or instructions for use; the ICD, DHHS-approved sample informed consent document; the complete DHHS-approved protocol.

The entire submission is available to all members in eIRB system for review. If an IRB member requires additional information to complete the review they may contact the RPO Coordinator and/or the RPO Director or Manager to make the request of the investigator. In instances where the reviewer feels it necessary, they may contact the investigator directly.

3.6.6 Quorum

A quorum consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. The nonscientist's attendance is required as part of quorum. All members, including the unaffiliated member, are expected to attend a minimum of 8 out of 12 meetings per year. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. The IRB Chair, with the assistance of the IRB staff, will confirm that an appropriate quorum is present before calling the meeting to order. The IRB Chair will be responsible to ensure that the meetings remain appropriately convened.

Quorum must be maintained for each vote to occur. The Research Protection Office Coordinator takes note of arrivals and departures of all members and notifies the chair if a quorum is not present. If a quorum is not maintained, the proposal must be deferred or the meeting must be terminated. A member may abstain from a vote (e.g. if they were not present for the entire discussion) and still count towards quorum. However, members who recuse themselves (e.g. because of a conflict of interest) are not counted towards quorum.

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

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

3.6.7 Meeting Procedures

The IRB Chair, or Associate Chair, in the event that the IRB Chair is absent, will call the meeting to order, once it has been determined that a quorum is in place. The Chair or Associate Chairs will remind IRB members to complete the COI forms and recuse themselves from the discussion and vote by leaving the room when there is a conflict.

The IRB will review and discuss the IRB Minutes from the prior meeting and determine if there are any revisions/corrections to be made. If there are no changes to be made, the Minutes will be accepted as presented and considered final. If it is determined that revisions/corrections are necessary, the Minutes will be amended and presented at the following IRB meeting.

The convened IRB reviews all full board submissions for initial and continuing review, as well as requests for modifications. The Primary Reviewers present an overview of the research. All members present at a convened meeting have full voting rights, except in the case of a conflict of interest (see 2.9). In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

It is the responsibility of the IRB coordinator to record the proceedings of the session for taking minutes at each IRB meeting.

3.6.8 Guests

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

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the Research Protection Office Director. Guests may not speak unless requested by the IRB and if not affiliated with Lifespan, they may be asked to sign a Lifespan confidentiality agreement.

3.7 Criteria for IRB Approval of Research

In order for the IRB to approve human subject's research it must determine that 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.

(3) Selection of subjects is equitable.

(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.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR§46.117.

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

The Criteria letter will be presented to the members prior to vote and the members vote will be based on meeting the criteria.

3.7.1 Risk/Benefit Assessment (1)(2)

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.

The goal of the assessment is to ensure that the risks to research subjects posed by participation in the research are justified by the anticipated benefits to the subjects or society.

Toward that end, the IRB must:

1. Judge whether the anticipated benefit, either of new knowledge or of improved health for the research subjects, justifies asking any person to undertake the risks;
2. Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.
3. Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
4. Determine whether the risks will be minimized to the extent possible;
5. Identify the probable benefits to be derived from the research;
6. Determine whether the risks are reasonable in relation to the benefits to subjects, if any, and assess the importance of the knowledge to be gained;
7. Ensure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;

3.7.2 Scientific Merit

Departmental scientific review is documented by the signature in eIRB system of the Department Chair, or designee determined by departmental chair, responsible for the investigator's research unit on new protocol applications in order to assess the risks and benefits of the proposed research:

1. The research uses procedures consistent with sound research design;
2. The research design is sound enough to reasonably expect the research to answer its proposed question; and

3. The knowledge expected to result from this research is sufficiently important to justify the risk.

The IRB may draw on the knowledge and disciplinary expertise of others, such as reviews by a funding agency, or departmental review.

3.7.3 Selection of subjects is equitable (3)

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

3.7.3.1 Recruitment of Subjects

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

3.7.4Data Safety Monitoring (6)

The IRB determines that, where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects. For research in which risks are greater than minimal risk, the IRB may require a general description of the data and safety-monitoring plan to be submitted to the IRB as part of the proposal.

In general, the risk assessment is performed by the IRB and may involve the following categories:

Low risk: Studies of this risk level are limited to those that involve innocuous procedures but no therapeutic agent. These may include survey research, questionnaires, blood sampling, or observational studies on non-vulnerable adults. It is usually sufficient for the PI to monitor these studies and the plan should include a minimum of annual progress reporting to the IRB.

Moderate risk: Studies of this risk level require a more detailed plan for patient safety monitoring and may include studies investigating a ‘safe’ therapeutic agent. These studies may require additional monitoring by a qualified medical monitor, safety officer, or an ad hoc safety committee.

High risk: High risk studies include: clinical trials using investigational agents including some Phase I studies; some Phase II studies; all Phase III comparative clinical studies; multicenter studies coordinated by a Lifespan investigator; investigator-initiated studies involving INDs, gene therapy studies, or other studies involving vulnerable

subjects. These studies may require a minimum of semi-annual reports plus additional monitoring measures as determined by the IRB, which may include monitoring by a Data Safety Management Board (DSMB), monitoring by a qualified medical monitor, or external oversight by an ad hoc safety committee.

All studies considered to be greater than minimal risk require a Data Safety Monitoring Plan (DSMP). DSMP's play an essential role in protecting the safety of participants, and assuring integrity of the study. They accomplish the former by being familiar with the protocol, proposing appropriate analyses, and periodically reviewing the developing outcome and safety data.

The plan must be appropriate to an individual study's objectives, design, and estimated risk level: The DSMP should specify the procedures employed to maximize participant safety throughout the study. Each plan should be tailored to fit the estimated degree of risk to the participant as well as the size and complexity of the study. Therefore, it is necessary to estimate the level of risk associated with the protocol, as this will drive the type of monitoring needed and the level of oversight required.

DSMB's, external to the investigator and sponsor, may be necessary for large, randomized multi-site studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome. In general, it is desirable for a DSMB to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions, generally Phase III studies are in this category. For some studies the National Institutes of Health (NIH) require a DSMB.

The IRB has the authority to require a DSMB or DSMP as a condition for final approval of research where it determines that such monitoring is needed. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide unanticipated problems/AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

The application for submission provides a minimum acceptable plan for all studies greater than minimal risk:

1. Adverse Events/Unanticipated Problems will be monitored for safety, trends, issues that may require stopping the study. This is considered a DSMP.
2. In a sponsored clinical trial, the sponsor will identify an individual, team or DSMB, depending upon the type and risk of study, who is responsible for monitoring as required above. A DSMB usually requires an independent outside consultant or board that will monitor independently of the sponsor. These types of boards are usually required for Phase III studies.
3. The sponsor will state they will report to regulatory agencies and IRBs in accordance with regulations.
4. The sponsor will indicate in writing how often safety review/monitoring will occur;

5. The sponsor has a pre-established set of rules/guidelines that spell out what actions they will take with regard to the safety information that they review (e.g., stopping rules; team meetings to modify protocol, etc.).

When the convened IRB reviews a DSMP and requests major modifications to the plan as presented, the investigator must comply with the IRBs requests and present the revised plan to the convened IRB for review and approval. If not presented at the initial convened meeting, approval will be deferred until the modifications are submitted for review at the next convened meeting.

3.7.5 Privacy and Confidentiality (7)

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

Definitions

- **Privacy** - having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.
- **Confidentiality** - methods used to ensure that information obtained by researchers about their subjects is not improperly divulged.
- **Private information** - information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
- **Identifiable information** – information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

3.7.5.1 Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are getting access to subjects or subjects' private, identifiable information and the subject's expectations of privacy in the situation.

3.7.5.2 Confidentiality

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

At the time of initial review, the IRB ensures that the privacy and confidentiality of research subjects is protected. The IRB assesses whether there are adequate

provisions to protect subject privacy and maintain confidentiality. The IRB does this through the evaluation of the methods used to obtain information:

a. About subjects,
b. About individuals who may be recruited to participate in studies
c. The use of personally identifiable records and
d. The methods to protect the confidentiality of research data. All research documentation must be kept according the Lifespan's corporate policy CCPM-55 which states all research records must be kept in locked secure cabinets in a locked secure room.

The PI will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research subjects is sufficiently protected.

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

3.7.5.3 Certificates of Confidentiality

In some cases, the IRB may also recommend or strongly recommend that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 17.1). Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. Certificates are granted sparingly. The study's funding source, if any, is not relevant to the decision. For most research, Certificates are obtained from NIH. If there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

3.7.6 Vulnerable Populations (8)

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity. The IRB carefully evaluates each protocol to determine if vulnerable subjects are included in the study population and what measures have been taken to protect them. This feature is included in the IRB application form and appendix for vulnerable subjects.

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

The IRB carefully considers group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects. Investigators are not permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.

The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that someone other than the primary care provider conduct the informed consent session and that additional measures for evaluating capacity to consent be in place.

In rare circumstances the IRB may require that the investigator submit each signed informed consent form to the IRB. The IRB may also require that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 6

3.8 Additional Considerations during IRB Review and Approval of Research

3.8.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either "minimal" or "greater than minimal" based on the "absolute" interpretation of minimal risk.

3.8.2 Period of Approval

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

3.8.2.1 Review More Often Than Annually

Unless specifically waived by the IRB, research that meets any of the following criteria may require review more often than annually unless waived by the IRB:

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

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The overall qualifications of the PI and other members of the research team.
4. The specific experience of the Responsible Investigator and other members of the research team in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events more likely.
7. Any other factors that the IRB deems relevant.

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

3.8.3 Independent Verification That No Material Changes Have Occurred

As provided for in its Assurance, an institution must prepare written procedures and guidelines to be followed by the IRB when conducting its initial and continuing review of research, and for reporting its findings and actions to the investigator and the administration of the institution.

- The procedures must provide guidance for determining which projects will require review more often than annually and which projects require verification from sources other than the investigator that no material changes have occurred since the last IRB review (45 CFR§46.103 b,4,ii).
- The guidelines must also delineate procedures for ensuring prompt reporting to the IRB, by the investigator, of proposed changes in a research activity.
- They must also provide procedures for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

To this end Lifespan has forms that adequately address the above that are required for submission of initial, revisions and continuing reviews.

3.8.4 Consent Monitoring

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

See Section 5.7 for a detailed discussion of consent monitoring.

3.8.5 Investigator Conflicts of Interest

The research application asks protocol-specific questions regarding conflict of interest for the investigators and key personnel. As part of its review process, the IRB will make a determination as to whether a conflict of interest exists with regard to the research under review. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict management plan, as determined by the COI Committee adequately protects the human subjects in the protocol is in place.
(See Section 14 for a detailed discussion of Conflict of Interest)

3.8.6 Significant New Findings

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

3.8.7 Advertisements

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

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

This information should be submitted to the IRB with the initial application or as an addendum to the protocol prior to implementation to assure that the information does not promise or imply a certainty of benefit beyond what is contained in the protocol and the informed consent document.

The IRB reviews the material to assure that the material is accurate and is not coercive or unduly optimistic.

The Investigator should exercise particular discretion when recruiting subjects as research participants. The recruitment material should be limited to the information the prospective subjects need to determine their eligibility and interest.

When using direct advertisement such as newspaper, radio, TV, internet/social media, bulletin boards, posters, and flyers that are intended for prospective subjects, no claims such as those listed below, should be made, either explicitly or implicitly.

Advertising for recruitment into investigational drug, biologic, or device studies should not use terms such as:

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

Such representation would not only be misleading to subjects, but would also be a violation of the Agency’s regulations concerning the promotion of investigational drugs [21 CFR§312.7(a)] and of investigational devices [21 CFR§812.7(d)].

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

1. The name and address of the clinical investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits (e.g. no cost of health exam).
8. Lifespan advertisements may state that subjects will be compensated, but should not state the payment or the amount to be paid.

Once these advertisements have been approved by the IRB placement of the advertisements should adhere to guidelines set down by each location. Advertisements

placed outside the Lifespan community, other than public bulletin boards/posters or paid ads; require a letter of collaboration be provided to the IRB.

Advertisements placed at one of the Lifespan affiliates and/or departments must adhere to the guidelines set down by each individual affiliate and/or department and may also require a letter of collaboration.

IRB review and approval of listings of clinical trials on the intranet/internet is not required when the system format limits the information to: the title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the site for further information.

Examples of clinical trial listing services that do not require prospective IRB approval include:

The National Cancer Institute's Clinical Trials listing

The government-sponsored DAIDS HIV/AIDS Clinical Trials Networks

Payment to Research Subjects

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

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

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

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

3.8.8 Recruitment Incentives

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from researchers (physicians) ("finder's fees") is not permitted.

3.8.9 Compliance with all Applicable State and Local Laws

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

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

3.9 Possible IRB Actions

Approval - the study is approved as submitted.

As per federal regulations, (45 CFR§46.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents. One is if study procedures are to be developed during the course of the research, but human subjects' approval is required by the sponsoring agency. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests. Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

Approval pending modifications - the protocol and/or consent form require minor revisions, such as wording changes, with replacement language provided. For full review, the needed revisions are agreed upon at the meeting, for expedited review, they are designated by the reviewer(s). These revisions are presented to the Principal Investigator for incorporation by simple concurrence.

In order to receive approval for a protocol requiring modifications:

1. For full review, the investigator's response, the revised protocol, with tracked changes, and the previously submitted protocol is given to the IRB Chair, Associate Chair, or designee, or a subcommittee of the IRB for review. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the IRB.
2. For expedited, the investigator's response, the revised protocol, with tracked changes, and the previously submitted protocol may be given to the same reviewer(s), or designee. The reviewer(s) may approve the study upon receipt and approval of the revisions without further action by the IRB.
3. Approval of the protocol application will not be granted and certification will not be issued until all deficiencies, if any, are corrected to the satisfaction of the IRB or the reviewer(s).

4. The outcome of the IRB's deliberations is once again communicated to the investigator in writing via the eIRB system.
5. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of the next IRB meeting or in the file for expedited review.

Note: For full review of new studies, the approval date is the date of convened IRB meeting. The accepted date is when the Chair/designee reviews and accepts IRB requested (non-substantive) corrections. The expiration date for the protocol is calculated based on the date that convened IRB reviewed the protocol and NOT on the accepted date.

Deferred for substantive issues regarding the protocol and/or consent form: This action is taken if substantial modification or clarification is required, or insufficient information is provided to judge the protocol application adequately (e.g., the risks and benefits cannot be assessed with the information provided). IRB approval of the proposed research must not occur until subsequent review of the material the PI submitted by the convened IRB.

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

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

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

3.10 Study Suspension and Termination

3.10.1 Suspension/Termination

A decision by the IRB or Chair may be made to suspend or terminate approval of research not being conducted in accordance with IRB or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. (See Section 8 for a discussion of unexpected problems and Section 10 for a discussion of non-compliance).

The IRB Chair may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair must be presented to the next convened IRB. Alternatively, the PI may choose to self-suspend his/her studies upon discovery of any unanticipated problem/complain/deviation, etc., which may present risk or the potential of risk to research participants or others. The convened IRB will evaluate the reason for the chairs emergent decision to suspend the study or the PIs decision to self-suspend. A review of the issues will be presented and discussed. The convened IRB will review the reason for suspension/termination; review the protocol, the current informed consent and either the initial application alone if new study, or initial application and a copy of the latest continuing review report. The IRB will vote on whether to suspend or terminate and this vote will be reflected in the meeting minutes.

When study approval is suspended or terminated, the IRB or the person ordering the suspension or termination must consider actions to protect the rights and welfare of currently enrolled subjects; and, considers whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring).

Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review. Research may only be terminated by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

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

When study approval is suspended or terminated by the convened IRB or the IRB Chair, in addition to stopping all research activities, any subjects currently participating in the study will be notified that the research has been suspended or terminated. Arrangements for medical care as needed, see above, will be considered.

All suspensions and terminations will be reported to the appropriate institutional officials and regulatory agencies according to the procedures in Section 11.

3.11 Continuing Review

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

3.11.1 Approval Period

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

For each initial or continuing approval the IRB will indicate an approval period with an approval expiration date specified. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB approved the research. For a study approved under expedited review, the approval period begins on the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

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

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires. Continuing Review Process

*When the IRB Reviews and Approves Research **With Conditions** at a Convened IRB Meeting Without Requiring Further Review at a Subsequent Convened Meeting.* In circumstances where the approval of continuing review required changes, the expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after that effective date of initial IRB approval (45 CFR§46.109(e)). OHRP notes that the first continuing review in these circumstances may occur earlier; for example, for logistical reasons an IRB may choose to set the expiration date of the initial approval period at one year from the date of the IRB meeting at which the research project initially was approved with conditions. See: http://www.hhs.gov/ohrp/policy/continuingreview2010.html#section-b1 for full explanation of review period for continuings.

3.11.2 Continuing Review Process

Continuing Review is accomplished by requesting the researcher submit a completed **Continuing Review Report**. A request for this report will automatically be sent by the eIRB system 90, 60 and 30 days prior to the due date for continuing review by the IRB. If no report is received, follow up with the investigator will be conducted by the ORA via email. These emails will inform the investigator that failure to submit a progress report

may lead to lapse of IRB approval and closure of the study. It is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review, as applicable:

- the current protocol along with a summary of the study as it is currently being conducted, including a brief description of any substantive changes that have been made since the initial approval
- the current consent document;
- any newly proposed consent document; and
- the form for continuing review
- all other applicable documents

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

3.11.3 Expedited Review of Continuing Review

In conducting continuing review under expedited review, the reviewer(s) are shared with the entire submission. The reviewer(s) complete the IRB Reviewer Form or adds checklist to comment section which indicates all criteria as per 45 CFR§46.111 and 21 CFR§56.111, have been met and approval granted.

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

3.11.4 What occurs if there is a Lapse in Continuing Review?

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

The Research Protection Office is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

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

Failure to submit continuing review information on time and continuing to conduct research after IRB approval has expired is non-compliance and will be handled according to the non-compliance policy (See Section 10).

If a continuing review report form has not been received within 30 days of IRB approval expiration the study will be administratively closed. The IRB may require the investigator to furnish information regarding patient follow up if applicable. The investigator is responsible to locate another investigator conducting the same study to follow his/her patients once IRB approval has expired.

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 30 days and the PI has not provided the required continuing review information, the PI may be required to submit a new application to the IRB for review and approval. If the study approval has lapsed 30 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

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

3.12 Amendment of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes in approved research** - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the subject (in which case the IRB must then be notified within 5 working days).

Modifications may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, a modification request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. Investigators must submit documentation to inform the IRB about the changes in the status of the study, including, but not necessarily limited to:

- Completed “Request for Revision to Protocol” form;
- Revised Investigator’s protocol application or sponsor’s protocol (if applicable)
- Revised approved consent/parental permission/assent documents (if applicable) or other documentation that would be provided to subjects when such information might relate to their willingness to continue to participate in the study
- Revised or additional recruitment materials
- Any other relevant documents provided by the investigator

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

3.12.1 Exempt Research.

Any changes that are made to an exempt approved protocol must be submitted for review by the IRB prior to implementation. Some modifications to the research may change the review status and require the previously exempt approved research application now be reviewed for expedited or full Committee review.

3.12.2 Expedited review of Protocol Modifications

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

The reviewer(s) complete the IRB Reviewer Form or adds checklist to comment section in eIRB system which indicates all criteria, as per 45 CFR§46.111 and 21 CFR§56.111, have been met.

3.12.3 Full Board Review of Protocol Modifications

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed within 5 days of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

All IRB members are shared on the package and review the request for revision and all documents submitted by the investigator.

At the meeting, the Primary Reviewer presents an overview of the modifications and completes the Reviewer form which indicates that all criteria for approval have been met.

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

3.12.4 Revisions That Require Re-consent/Notification of Participants:

The IRB will render a determination of whether the changes to the research activities require a change in the informed consent and therefore warrant re-consenting of currently enrolled participants or notification of participants who have completed research interventions.

In the event that new information becomes available during the course of a clinical research investigation which directly affects the rights and/or welfare of the human subjects enrolled in the investigation; or where the new information represents increased risk to study volunteers, then the principal investigator or designee should:

- As soon as possible, and within 5 working days, submit new information and any patient notification materials for IRB review and approval unless immediate hazard to the participant warrants reporting
- If appropriate, submit adverse event reports to IRB.
- Notify enrolled subjects

3.13 Closure of Protocols (end of study)

The completion or termination of a study must be reported to the IRB. Investigators may submit a progress report to the IRB for close-out or termination either at the time of continuing review or earlier as applicable.

The Research Protection Office staff will review the termination report for completeness. Closure reports from the sponsor may be submitted with the final progress report, if applicable.

3.14 Reporting IRB Actions

All IRB actions are communicated to the Principal Investigator and/or designated primary contact person for the protocol, in writing via the eIRB system within ten (10) working days of final action via a template letter prepared by the IRB staff, and sent through the e-IRB system. The approval notification will include stamped approved consent and ads when applicable. When the IRB defers a protocol or grants approval pending modifications, the notification will include the modifications required for approval along with the basis for requiring those modifications. For deferrals,

disapproval, termination or suspension, the notification will include the basis for making that decision.

The IRB reports its findings and actions to the institution in the form of its minutes, which are distributed by IRB staff to the Lifespan Institutional official and are stored permanently and securely in the e-IRB system.

3.15 Appeal of IRB Decisions

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

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

4 Documentation and Records

4.1 IRB Records

The IRB, through the eIRB system, retains copies of all research protocols and supporting documentation, minutes of IRB Committee meetings, documentation of continuing review activities, any significant new findings to be provided to participants, and correspondence between the IRB, administration, Investigators, and any appropriate Federal and/or state agency. The IRB serves as a liaison for regulatory or institutional information between Investigators, sponsors, institutional administration, and OHRP/FDA.

The IRB must prepare and maintain adequate documentation of the IRB's activities. Since conversion to an eIRB system that is 21 CFR§11 certified all records submitted and reviewed are retained indefinitely. The records include but are not limited to:

- The initial IRB application;
- All items reviewed;
- Relevant IRB meeting minutes and any email correspondence related to those minutes;
- Revised IRB applications;
- Final approval letters;
- Current date stamped informed consent documents;
- Amendments;
- Applications for continuing review;
- Advertisements and other recruitment materials in paper format;
- Legal opinions;
- Letters of correspondence
- Electronic mail correspondence or other modes of communication directly impacting research activity review or change.
- Letters of cooperation from performance sites;
- IRB approvals from collaborating institutions or performance sites;
- Collaborating institutional agreements;
- Approval letters from other Committees (e.g., Biosafety, RDC, etc.);
- All IRB Education/Compliance team auditing reports including compliance reviews and quality assurance (QA) reports.
- Adverse event reports;
- Protocol deviation reports;
- Data safety monitoring reports, including DSMB, DSMC, or DSM reports; and
- Any sponsor's monitoring and auditing reports that were submitted by the investigator/sponsor
- All "Reviewer's Comment Forms," including those from external consultants;
- All vulnerable population documentation.
- Grant applications;

- Investigator's brochures;
- Sponsor's protocols; and
- Other supporting documents (journal articles, publications, etc).
- Reports of injuries to subjects
- Unanticipated problems involving risks to subjects or others

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

- Waiver or alteration of the consent process.
- Research involving pregnant women, fetuses, and neonates.
- Research involving prisoners.
- Research involving children.

If a protocol is cancelled without subject enrollment, IRB records are maintained for at least three years after cancellation. (The eIRB system does not allow any record to be deleted once it has been submitted and approved/deferred or disapproved by the IRB).

4.2 IRB Membership Roster

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

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

9. Alternate status, including the member they alternate with
10. Relationship (e.g., employment) between the individual IRB member and the organization

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

4.3 The IRB Minutes

A template for the meeting minutes will be used for Minutes documentation. Proceedings must be written and available for review by the next regularly scheduled IRB meeting date. Once approved by the members at a subsequent IRB meeting, the minutes, if altered for any reason, must be re-reviewed by the IRB for approval.

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
    a. Names of members present
    b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing were able to actively and equally participate in all discussions
    c. Names of absent members
    d. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster)
    e. Names of consultants present
    f. Name of investigators present
    g. Names of guests present

    Note: The initial attendance list shall include those members present at the beginning of the meeting. The minutes will indicate, by name, those members who enter or leave the meeting. The vote on each action will reflect the number of members present for the vote on that item.
2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. Business Items discussed
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing initial review, continuing review, or review of modifications by the convened IRB
6. Votes on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused). The minutes will record who recused and for what reason.
7. Basis or justification for these actions including required changes in research

8. Summary of controversial issues and their resolution
9. Approval period for initial and continuing approved protocols
10. Risk level of initial and continuing approved protocols
11. Review of interim reports, e.g. Adverse Event or Safety Reports, Amendments, Report of violation, etc. that have been referred to the full board.
12. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR§46, the Minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts or the IRB's agreement with the findings and justifications as presented by the investigator on IRB forms.
13. Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.
14. A list of research approved since the last meeting utilizing expedited review procedures and the specific citation for the category of expedited review of the individual protocol.
15. Documentation of approval by the Chair or designee of research contingent on specific minor conditions in the Minutes of the first IRB meeting that takes place after the date of the approval. (appears under expedited review)
16. An indication that, when an IRB member has a conflicting interest (see Section 2.3.2) with the research under review, the IRB member recused and was not present during the deliberations or voting on the proposal, and that the quorum was maintained.
17. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant

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

4.4 Documentation of Exemptions

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

4.5 Documentation of Expedited Reviews

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

4.6 Record Retention

The above detailed records, pertaining to research which is conducted, must be stored securely in the Research Protection Office and must be retained for at least 3 years. IRB records not associated with research or for protocols cancelled without participant enrollment will be retained at the facility for at least 3 years after closure.

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

Remaining paper records are maintained in a secured, archived, off-site location and are available to IRB members and Research Protection Office staff within 24 hours or sooner if necessary. Electronic research records have no paper based record and are maintained in the e-IRB system indefinitely.

4.7 Record Retention for Investigators

To meet record retention obligations Lifespan requires investigators to maintain research records for a minimum of 6 years after completion of the research study. This requirement is based on state and federal laws and regulations.

- RI state law to maintain research records for 5 years after completion of the research study;
- FDA requires maintaining records for 2 years after approval of the investigational product;
- OHRP requires 3 years after termination of the study; and,
- HIPAA states a patient in a covered entity should have access to their records for a minimum of 6 years. These records include research records.

Research records must be maintained in locked cabinets behind locked or secured doors. Electronic research data must be maintained on a password protected computer. Only Lifespan required thumb drives or Lifespan managed computers are to be used for storing electronic data.

Investigators are to abide by the Lifespan corporate policy CCPM-55 “Policy Regarding Incidental Disclosure of Protected Health Information” which states under III(h) “…research documentation…should be secure, kept in locked cabinets behind locked or secured doors for the duration.

5 Obtaining Informed Consent from Research Subjects

5.1 Policy

Researchers (PI or designate) will explain the purpose of the study to the prospective subject or their authorized representative. He or she will explain how the study will be carried out and what the prospective subject will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. The prospective subject must be given the opportunity to ask the researcher any questions about the research before consenting to take part in the study. This process is called informed consent. No investigator may involve a human being as a participant in research unless the investigator has obtained the legally effective informed consent of the participant or the participant's legally authorized representative.

Researchers may seek consent only under circumstances that provide the prospective subject or his or her representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. Furthermore, the information must be written in language that is understandable to the subject or representative. The consent process may not involve the use of exculpatory language. This means that the consent form must not include language that tends to imply to the participant that they waive or appear to waive any of their legal rights, or releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence.

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

5.2 Definitions

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

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

5.3 Basic Requirements

No investigator may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 5.8 of these procedures and in accordance with state and Federal laws.

Except as waived or as provided in Section 5.9 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB (See Section 5.6).Investigators must obtain consent prior to entering a subject into a study and/or conducting any procedures required by the protocol, unless consent is waived by the IRB.

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

5.4 Informed Consent Process

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, consent must be obtained from a legal guardian or a legally authorized representative.
2. The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to consider whether or not to participate.
3. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
4. The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated to 8th grade level and layman's terms shall be used in the description of the research.
5. For subjects whose native language is not English, (i) the oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

All English IRB approved consents that are translated into another language must be submitted to the IRB for review and approval with written verification from the translator of the translation.

6. The consent process may not involve the use of exculpatory language. This means that the consent form must not include language that tends to imply to the participant that they waive or appear to waive any of their legal rights, or releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence.
7. The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

5.5 Basic Elements of Informed Consent

A. The following elements are required in all consent forms unless waived by the IRB (see Section 5.8):

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the expected duration of the subject's participation, a description of the **procedures** to be followed, and identification of any procedures which are experimental; a description of any reasonably foreseeable **risks** or discomforts to the subject;
2. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
3. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
4. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained;
5. For research involving more than minimal risk, an explanation as to the availability of medical treatment in the case of **research-related injury**, including who will pay for the treatment and whether other financial compensation is available;
6. An explanation of whom to contact on the research team for answers to pertinent questions about the research or to voice concerns or complaints about the research, and whom to contact in the event of a research-related injury to the subject;
7. Contact information for the IRB to obtain answers to questions about the research; to voice concerns or complaints about the research; to obtain answers to questions about their rights as a research participant; in the event the research staff could not be reached; and in the event the subject wishes to talk to someone other than the research staff.
8. A statement that participation is **voluntary**, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled;

9. For **FDA-regulated studies**, the possibility that the Food and Drug Administration may inspect the records needs to be included in the statement regarding subject confidentiality.

B. The following elements are required if appropriate to the research:

1. A statement that the particular treatment or procedure may involve risks to the subject, which are currently unforeseeable. (For example: Include when the research involves investigational test articles or other procedures in which the risks to subjects is not well known.)
2. A statement that if the subject is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable. (For example: Include when the research involves pregnant women or women of childbearing potential and the risk to fetuses of the drugs, devices, or other procedures involved in the research is not well known.)
3. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. (For example: Include when there are anticipated circumstances under which the investigator may terminate participation of a subject.)
4. Any additional costs to the subject that may result from participation in the research. (For example: Include when it is anticipated that subjects may have additional costs.)
5. The consequences of a subject's decision to withdraw from the research. (For example: Include when withdrawal from the research is associated with adverse consequences.
6. Procedures for orderly termination of participation by the subject. (For example: Include when the protocol describes such procedures.)
7. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. (For example: Include when the research is long term and interim information is likely to be developed during the conduct of the research.)
8. The approximate number of subjects involved in the study. (For example: Include when the research involves more than minimal risk.)
9. In some circumstances, the Lifespan Research Conflict of Interest Committee may, through its deliberations, recommend particular language to the IRB that addresses a relationship between the investigator and other parties. This language will be placed into the informed consent document.
10. When following Department of Defense regulations, the IRB determines that the disclosure includes that provisions for research-related injury follow the requirements of the Department of Defense component.

C. Participant withdrawal from study

When participants withdraw from a clinical trial, IRB determines:

1. When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remains part of the studydatabase and may not be removed. The consent document cannot give the participant the option of having data removed.
2. A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the participant's information.
3. The researcher must obtain the participant’s consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB must approve the consent document.
4. If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

5.6 Documentation of Informed Consent

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

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent.

2. A copy of the consent form must be given to the person signing the form.

3. The consent form may be either of the following:

    a. A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read by or to the subject or the subject's legally authorized representative, but the subject or representative must be given adequate opportunity to read it before it is signed; or

b. A short form written consent document for non-English speaking Research Participants stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. Refer to Section 5.10.1 for additional details about short form consent documents.

   When this method is used:
   i. there must be a witness to the oral presentation; and
   ii. the IRB must approve the main consent form and the use of the short form; and
   iii. the witness, the participant and the person obtaining consent must sign both the short form and a copy of the main consent form; and
   iv. a copy of the main consent must be given to the subject or representative, in addition to a copy of the short form.

4. All consent forms for studies that seek to enroll study volunteers into clinical research conducted at Lifespan affiliates must use the appropriate Lifespan template.

5. All consent forms for studies that seek to enroll study volunteers into Lifespan sponsored research conducted at non Lifespan affiliated sites may use a modified template to meet local requirements (i.e. international research).

5.6.1 Lifespan IRB Consent Form Template

Informed consent documents must include the following basic sections:

1. Nature and Purpose of the Project
2. Explanation of Procedures
3. Discomforts and Risks
4. Benefits
5. Alternative Therapies
6. Refusal/Withdrawal
7. Medical Treatment/Compensation in Case of Injury
8. Rights and Complaints
9. Confidentiality and Research Authorization for Use and Disclosure of information

Optional Sections

Clinical Trials as applicable
HIV and GINA language as applicable

Participation in Specimen Banking

Specific instructions for the content to be included under each heading can be found in the template for consents.

Header

The Lifespan Logo may be inserted on the first page header of the informed consent form (ICF) or the ICF may be printed on institutional letterhead. Each page must include the study volunteer's initials to document that the study volunteer has received each page of the ICF.

Footer

The footer contains safeguards to insure the researcher and study volunteer have signed the correct and read the complete document.

The left-hand side of the footer includes the version date of the consent template (the date the template was created by the RPO). The short title should be included below the version date. The short title may include a sub category such as "control group", "relative" etc. to further delineate the appropriate consent form.

In the middle of the footer is the page number. The IRB prefers the format that indicates the page number and the total number of pages of the consent (i.e. 1 of 10).

The right-hand side should contain the most recent protocol version date, amendment date, or if none of those are applicable, the most recent date the consent was created. A date format that prevents automatic dating should be used.

Please note the minor informed consent template is to be used for protocols involving children as subjects of research. The introductory paragraphs as they appear in the sample consent forms MUST be included, except in the Adolescent/Child Assent Forms. The numbered items listed in the template must be addressed as they apply to the research protocol. Certain verbatim wording is required and cannot be changed as noted in the template.

If there are multiple consents for the same study -the use of colored paper or subtitles is recommended to ensure the correct ICF and/or ICF version is used.

5.6.2. Authorized Variations of the Standard Consent Form Template

5.6.2.1Adolescent/Child Assent Forms

The assent document is required unless waived by the IRB for underage subjects (8-17 years of age) who are unable by law to sign their own informed consent document. Often the child does not read or is not able to understand the parent/guardian permission (consent) form. This document allows the child to

understand what the study is about and what the child can expect if s/he participates in the study.

Assent documents include the basic elements of the parent/guardian informed permission (consent) document but describe the information in a narrative form with or without headings (a sample assent form is provided in the eIRB forms library). Wherever possible, the assent form should use language that is simpler than the parent/guardian permission (consent) form. The boilerplate preamble contained on the consent form is eliminated from the assent form

A signature line on the assent form is not required. The child or adolescent may sign the assent line on the accompanying parent/guardian permission (consent) form if the child is old enough to read and understand the consent form.

5.6.2.2NCI (National Cancer Institute) Cancer Consent Format

The NCI cancer consent format used by oncology researchers may be used instead of the standard Lifespan consent format. The Lifespan affiliate IRBs have reviewed modified and approved the use of this format. The IRBs agree that the format is simple and straightforward and enhances the readability and understanding of those subjects seeking to enroll in complicated oncology research protocols.

5.6.2.3Specimen Banking Language

Purpose:

The purpose of this policy is to provide information, clarity and instruction to members of the research community regarding documentation that is required when Covered Researchers wish to obtain, use or disclose human subjects' specimens such as blood, body fluid or tissues for research purposes.

Eligibility:

This policy applies to all principal investigators, co-investigators, and all others responsible for the design, conduct or reporting of research (referred to as "Covered Researchers") that is conducted at or funded by Lifespan or any of its hospitals, or that is reviewed by any Lifespan review committee.

Policy:

Lifespan requires that research subjects agree to participate in banking their specimens whenever an identifiable specimen is going to be gathered for future studies, whether they are currently planned or unplanned. If a specimen is collected as part of an ongoing study and future tests on the specimen are planned as part of that *same* study, then adding the specimen banking language is not required, so long as the tests were covered in the protocol, consent form and other relevant

documents reviewed by the Lifespan IRB. If the future tests are merely related, (e.g., the Main study involves taking an investigational drug for HIV and blood is being banked for future unknown tests on HIV this would be considered merely related) to the ongoing study, then you must include Specimen Banking language in the consent form.

It is important to note that the term "identifiable" as used in this policy means that the specimen retains at least one of the eighteen (18) identifiers cited in the Health Insurance Portability and Accountability Act ("HIPAA") to be considered "de-identified", specimens must be permanently stripped of all of these identifiers. **"Coded" specimens where the researcher maintains the ability to break the code, or to otherwise create a link between the specimen and the subject's protected health information are considered identifiable**.

The purpose of the Specimen Banking language is to provide the subject with basic information about what the banking will entail and to provide a vehicle for the subject to provide HIPAA authorization for the banking activity. Under HIPAA, it is now permissible to combine authorization for the specimen banking with authorization for the underlying clinical trial.

Appropriate Specimen Banking language is optional as applicable and can be found in the template consent form in the eIRB system.
Alternatively, at some point in the future, the outside entity is free to ask Lifespan to contact its patients/research subjects to ask whether they wish to be put in contact with the outside entity to obtain information about and/or be consented for future research projects to be conducted by that outside entity. In such a case, Lifespan would either give the patient/subject the contact information of the outside entity, or document that the patient/subject authorized the outside entity to contact them directly.

Absent specific patient/subject authorization or waiver from the IRB, Lifespan will not release any fully identifiable protected health information to a specimen banking entity. Such authorization must be specific both as to the type of information to be disclosed and as to the nature of the study. (The IRB may waive authorization for a limited data set (LDS) if a data use agreement has been put into place. A limited data set may contain, for example, dates of birth, dates of death, dates of service, Town or city, State, Zip code. There are specific data a LDS may <u>not</u> include such as: name, Postal address information, other than town or city, State, and zip codes, telephone numbers, fax numbers, electronic mail addresses, Social security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers, vehicle identifiers and serial numbers, including license plate numbers, device identifiers and serial numbers, web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, biometric identifiers, including finger and voice prints; and, full face photographic images and any comparable images).

Procedure:

If a person has a *question concerning* the *interpretation or applicability* to a particular circumstance of any of the laws or regulations referred to in this Policy, such person should first consult with his/her supervisor(s) and if his/her supervisor(s) is unable to answer the question or provide any guidance or, if, because of the circumstances, it would be inappropriate to discuss the matter with his/her supervisor(s), then such person should contact the Office of Research Administration or the Office of the General Counsel for advice. If any person is aware of any violation or threatened or potential violation of this Policy, or *suspects* a violation of this Policy has occurred, such person must refer to the Policy on Code of Conduct for instruction as to what action to take. No adverse action will be taken against any party who reports, in good faith, any violation or apparent or threatened violation.

5.6.3IRB Approval and Expiration Dates on Consent Documents

The IRB will affix the approval, the accepted and the expiration dates on all approved informed consent documents. Copies of the current, dated documents are the only versions that may be used by Investigators in obtaining consent. This procedure helps assure that only the current, IRB-approved informed consent documents are presented to participants and serves as a reminder to the Investigators of the need for continuing review.

Continuing review materials should be submitted at least one month prior to expiration to avoid lapse in approval. Once the newly stamped informed consents are approved by the IRB, these documents must be used for consenting purposes.

5.7 Consent Monitoring

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

Such monitoring may be particularly warranted for:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving highly vulnerable populations (e.g., ICU patients, children)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or
- Other situations when the IRB has concerns that consent process is not being conducted appropriately.

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

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

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

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

5.8 Waiver of Informed Consent

Policy: There are circumstances under which the Federal regulations give the IRB the authority to waive or alter the required informed consent process (45 CFR§46.116). However, please be aware that, in some situations, RI State laws and regulations go beyond Federal law in limiting the IRB's ability to waive informed consent in its entirety. Pursuant to state law, other than an "emergency research situation", as defined by state and Federal law, the IRB will not consider issuing a complete waiver of informed consent for any research intervention (as defined by Federal Law) that would be performed while the subject was a patient of a Lifespan hospital; this would apply regardless of whether the Federal criteria for waiver could be met.

Please see Rhode Island General Laws Sections 5-37.3-4 and 23-17-19.1, and RIDOH Rules and Regulations for Licensing of Hospitals, especially Section 16(all linked below).
http://sos.ri.gov/documents/archives/regdocs/released/pdf/DOH/5407.pdf
http://webserver.rilin.state.ri.us/Statutes/TITLE5/5-37.3/5-37.3-4.HTM;http://www.rilin.state.ri.us/Statutes/TITLE23/23-17/23-17-19.1.HTM

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

a. The research involves no more than minimal tangible or intangible risk to the subjects;

b. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
c. The research could not practicably be carried out without the waiver or alteration; and
d. Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

Alternatively, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that all of the above apply plus:

a. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
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.
v. The research could not practicably be carried out without the waiver or alteration.

FDA regulations do not provide for waivers of informed consent except in emergency uses.

5.9 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects (45 CFR§46.117) if it finds either that the:

1. Only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, and the research is not FDA-regulated (Note: This option is not available for FDA regulated studies);
   or
2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to

require the investigator to provide subjects with a written statement regarding the research.

5.10 Informed Consents of Non-English Speaking Research Participants

Department of Health and Human Services regulations for the protection of human subjects require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (45 CFR§46.116 and §46.117).

Where informed consent is documented in accordance with §46.117(b) (1), the written consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with a consent document written in a language understandable to them.

Alternatively, §46.117(b)(2) permits oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary.

Participants who do not speak English should be presented with a consent document written in their native language. This is preferred. All English IRB approved consents that are translated into another language must be submitted to the IRB for review and approval with written verification of the translation by the back translation method, from the translator.

Federal regulations permit oral presentation of informed consent in conjunction with a short form written document. (i) The oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. A short form for use with Non-English Speaking participants has been translated into multiple languages. These short forms are available in the e-IRB system forms library.

Due to HIPAA authorization requirements at the time of consent, (i) both the short form document and the summary (i.e., the English language informed consent document)should be signed by the subject (or the subject's legally authorized representative), by the person obtaining consent as authorized under the protocol; and by the witness. When the person obtaining consent is assisted by a translator, the translator should sign on the translator signature line of the summary document.

The IRB must receive all foreign language versions of the short form document, not already provided by the RPO, along with verification of translation. Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

An English version of the template short form is available in the eIRB system for translating if language required is not already available

5.11 Documentation of Authorization to Use and Disclose PHI

When collecting identifiable protected health information, (PHI), the investigator must obtain authorization to Use and Disclose Research data. The combined Informed Consent (IC) document includes the authorization along with the Informed consent elements as required by HIPAA, OHRP and FDA. Only one signature on the IC document is required to obtain consent from the participant to be enrolled into the research study as well as authorization to use and disclose the research data collected from this study. Study participants will be given a copy of their signed informed consent document, which will include their authorization, as indicated in 5.6 of this section.

6. Vulnerable Subjects in Research

6.1 Policy

The federal regulations require that IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, fetuses, cognitively impaired persons, students, or economically or educationally disadvantaged persons [Federal Policy 45 CFR§46.111]. The following procedures describe the requirements for involving vulnerable participants in research under the auspices of Lifespan.

6.2 Definitions

Children, under Federal law (*see* 45 CFR§46.402), 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". Under the Federal law, if the research subject is a "child", the protections of Subpart D must be applied; if the subject is not a "child", Subpart D does not strictly apply. This Federal definition of "child" defers to Rhode Island state law. In general, under RI state law, the term "child" does not apply to anyone who is 18 or over. State law also contains certain exceptions that would empower persons under 18 to make some treatment decisions, such as in the area of substance abuse treatment (if the state law requirements are met), or treatment for communicable diseases, including HIV/AIDS. If a state law exception applies, the research subject would not be considered a "child" to which Subpart D would necessarily apply, although, for subjects under 18, an IRB might voluntarily apply certain Subpart D protections as deemed appropriate (such as for studies that involve more than minimal risk). All questions about whether a research subject is a "child" should be referred to the Director/Manager of the Lifespan Research Protection Office, who will involve the Lifespan Legal Department as necessary.
NOTE: For research conducted in jurisdictions other than Rhode Island, the research must comply with the laws regarding the legal age of consent in the local jurisdiction. If some of the research procedures occur in Rhode Island, Rhode Island law might also apply.

Legal Guardian means an individual who is authorized under applicable State or local law to consent on behalf of an incapacitated adult (see generally RIGL Chapter 33-15) or child (see generally Chapter 33-15.1) to general medical care. With respect to children, the parents are the natural guardians, and are the decision-makers unless their parental rights have been terminated (termination of parental authority can be partial) and another guardian has been appointed. Except in the case of parents, all

guardians in Rhode Island must be appointed or approved by the probate court. In the case of a court appointed or approved guardian, it is important to look at the scope of the guardianship to determine whether the guardian's authority extends to health care decision-making. Generally, this will necessitate looking at the court document that established the guardianship. The Lifespan Office of the General Counsel should be consulted if there are questions. Guardians with power to make health-care decisions under Rhode Island law, meet the definition of "Guardian" under 45 CFR§46.402 (e) as indicated above.

NOTE: For research conducted in jurisdictions other than Rhode Island, the research must comply with the laws regarding guardianship in all relevant jurisdictions. The Lifespan Office of the General Counsel will provide assistance with regard to the laws in other jurisdictions.

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

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

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

Neonate means newborn.

Nonviable neonate means a neonate after delivery that, although living, is not viable.

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

Viable neonate means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of being independently maintaining heartbeat and respiration. If a neonate is viable for purposes of 45 CFR§46.202, subpart B, then it may be included in research only to the extent permitted and in accordance with the requirements of 45 CFR§46.202 subparts A and D.

In vitro fertilization is any fertilization of human ova, which occurs outside the body of a female.

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

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

6.3 Involvement of Vulnerable Populations

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

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

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

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

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

6.4 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. The PI is responsible for identifying patients who are at risk for impaired decisional capacity and determining capacity for consent who are being asked to participate in a research study with greater than minimal risk.

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

6.5 Procedures

6.5.1 Initial Review of Research Proposal:

1. The PI should identify the potential to enroll vulnerable subjects in the proposed research at initial review and provide the justification for their inclusion in the study.
2. The IRB evaluates the proposed plan for consent of the specific vulnerable populations involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives.
3. The IRB evaluates and approves the proposed plan for the assent of participants.
4. The IRB evaluates the research to determine the need for additional protections and consider the use of a data and safety monitoring board/plan or committee as appropriate.
5. The PI should provide appropriate safeguards to protect the subject's rights and welfare, which may include the addition of an independent monitor. The independent monitor is a qualified individual not involved in the research study who will determine the subject's capacity to provide voluntary informed consent.
    a. Examples of studies that warrant independent monitoring include those involving schizophrenic patients who will be

exposed to placebo, and/or drug washout, and/or treatment with agents that are not approved by the Food and Drug Administration (FDA). Populations requiring independent monitoring would include individuals characterized by lack of reality testing (i.e., psychosis). Populations not usually requiring independent monitoring would include those with substance use disorders.

6. The IRB will assess the adequacy of additional protections for vulnerable populations provided by the PI.

6.5.2 Continuing Review and Monitoring:

At Continuing review the PI should identify the number of vulnerable subjects enrolled.

6.6 Research Involving Pregnant Women, Human Fetuses and Neonates

6.6.1Research Involving Pregnant Women or Fetuses

45 CFR Subpart B applies to all research involving pregnant women. Under 45 CFR§46.204, pregnant women or fetuses may be involved in research funded by DHHS 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 than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in

accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(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.

6.6.2 Research involving neonates

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 is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

6.6.2.1 Neonates of Uncertain Viability

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

The IRB determines that:

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

6.6.2.2 Nonviable Neonates

After delivery, nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

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

6.6.2.3 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of IRB Review Process and Research Involving Children.

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

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

6.6.4 Research Not Otherwise Approvable

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

1. That the research in fact satisfies the conditions of Section 6.6.1, as applicable; 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 accord with sound ethical principles; and
   c. Informed consent will be obtained in accord with the provisions for informed consent and other applicable sections of this manual.

6.7 Research Involving Prisoners

Prisoners are another of the three classes that are deemed so vulnerable to exploitation in research that there are special rules protecting them. In the past, prisoners were viewed as a convenient research population. They are housed in a single location, constitute a large and relatively stable population, and live a routine life. Unfortunately, all the things that make a prison and prisoners a convenient research population also make prisoners ripe for exploitation. The purpose of this policy and the

regulations at 45 CFR§46, Subpart C is to provide additional protections for research involving prisoners to protect them from exploitation.

“Prisoner” as defined above in section 6.2 and in 45 CFR§46.303(c). The Miriam Hospital IRB is currently the only Lifespan affiliated IRB constituted to review research involving prisoners. All research conducted under the auspices of any Lifespan affiliate involving prisoners, must be reviewed and approved by The Miriam Hospital IRB.

6.7.1 Applicability.

The additional protections required by Subpart C and this policy must be observed with respect to all biomedical and behavioral research conducted under the auspices of Lifespan involving prisoners as subjects. This includes situations where a human subject becomes a prisoner after the research has commenced. No research involving prisoners shall be approved unless it is specifically authorized within Subpart C and this policy. In addition, all research involving prisoners must accord with any applicable state or local regulations or policies, including but not limited to the Rhode Island Department of Corrections Policy Number 6.06-3 DOC pertaining to research, and any other regulations or policies promulgated from time to time by the Rhode Island Department of Corrections.

The exemptions at 45 CFR§46.101(b) do not apply to research involving prisoners. Research involving prisoners may be expedited, however, OHRP recommends that the convened IRB review research involving prisoners as human subjects.

6.7.2 Different Definition of Minimal Risk (See 45 CFR§46.303(d))

In addition to setting requirements about IRB composition and findings to be made in evaluating research proposals, Subpart C sets forth a definition of minimal risk that is different from the generally applicable definition found in Subpart A of the regulations (See 45 CFR§46.102 h (i)) In Subpart C, minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

6.7.3 Composition of the IRB (See 45 CFR§46.304(a) and (b))

An IRB reviewing research involving prisoners, in addition to satisfying the general requirements detailed in the IRB section of this manual and at 45

CFR§46.116 and §46.117, must meet the following compositional requirements:

- A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB.
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.
- The prisoner representative must be a voting member of the IRB.
    - The prisoner representative may be listed as an alternative member who becomes a voting member when needed.
- The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.
    - The prisoner representative must receive all review materials pertaining to the research (same as a primary reviewer).
- The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
    - The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting
- The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.
- Minor modifications to research may be reviewed using the expedited procedure described below, using either of the two procedures described based on the type of modification.
- Modifications involving more than a minor change reviewed by the convened IRB – must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).
- Continuing review – must use the same procedures for initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

- If no subjects have been enrolled, the research may receive continuing review using the expedited procedure under expedited category # 8.

In the absence of choosing someone who is a prisoner or has been a prisoner, the IRB should choose a prisoner representative who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner.

6.7.4 Additional Duties of the IRB (45 CFR§46.305(a))

In addition to all other responsibilities prescribed for the IRB under 45 CFR§46, Subpart A and in the Lifespan Institutional Review Board and IRB Review Process sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

1. The research under review represents one of the categories of research permissible under §46.306(a)(2);
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 Board will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7. Where the IRB finds there may be a need for follow-up examination or care of subjects 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 subjects of this fact.

6.7.5 45 CFR§46.306 Permitted research involving prisoners.

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

6.7.5 Waiver for Epidemiology Research

The Secretary of DHHS has waived the applicability of 45 CFR§46.305(a)(l) and 46.306(a)(2) for certain research conducted or supported by DHHS that involves epidemiologic studies and that meet the following criteria:
(1) In which the sole purposes are
(i) To describe the prevalence or incidence of a disease by identifying all cases, or

(ii) To study potential risk factor associations for a disease, and

2) Where the IRB has approved the research and fulfilled its duties under 45 CFR§46.305(a) (2)–(7) and determined and documented that

(i) The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and

(ii) Prisoners are not a particular focus of the research.

The specific type of epidemiological research subject to the waiver involves no more than minimal risk and no more than inconvenience to the human subject participants. The waiver would allow the conduct of minimal risk research that does not now fall within the categories set out in 45 CFR§46.306(a) (2).

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

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

6.7.6 Previously enrolled subjects

When a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by the institutional review board (IRB) in accordance with the requirements of HHS regulations at 45 CFR§46, subpart C, the principal investigator should promptly notify the IRB of this event. <u>All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.</u> The IRB will conduct a review of the research proposal in accordance with Subpart C and make one of the following determinations:

- IRB review and approval is not required if the research interactions and interventions or obtaining of identifiable private information will not occur during the incarceration period; or
- Approve withdrawal of the participant(s) from the study if withdrawal will not place the participant at undue harm or risk; or
- Since neither RIH IRBs are constituted under Subpart C to review research involving prisoners, should the continued participation of the now incarcerated subject be desirable, you must request the RPO transfer the study to The Miriam Hospital IRB for a Subpart C review. The IRB may require submission of updated documents. TMH IRB will become the IRB of record that will include the oversight of the application as research involving prisoners.

- TMH IRB shall document its deliberations in the minutes of the meeting that determines the appropriate category of allowable research under 45 CFR§46.306 and documents their findings under 45 CFR§46.305.

NOTE: OHRP has allowed one important exception. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

6.7.7 OHRP Certification

Under 45 CFR§46.305(c), for all research involving prisoners that is supported by HHS, the institution shall certify to the Secretary (through OHRP) in writing that the IRB has made the seven findings required under 45 CFR§46.305(a). Lifespan will send to OHRP a certification letter to this effect, which will also include the name and address of the institution and specifically identify the research protocol in question. As part of the package for OHRP, and as further required by OHRP, the institution shall also submit a copy of the "research proposal" so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR§46.306(a)(2), and if so, which one. The term "research proposal" includes the IRB-approved protocol, any relevant HHS grant application or proposal, the IRB application, and any other information requested or required by the IRB to be considered during initial IRB review.

The Director/Manager, Research Protection Office is responsible for ensuring that all required materials are forwarded to the DHHS.

Following receipt of the research proposal, OHRP will determine which, if any, of the four categories of research permissible under the HHS regulations at 45 CFR§46306(a) (2) the proposed research meets. OHRP will consult with appropriate experts with respect to certain research that falls under paragraphs (iii) and (iv) of 45 CFR§46.306(a) (2). When applicable, OHRP also will publish in the Federal Register a notice of intent to approve such research.

HHS conducted or supported research involving prisoners as subjects 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).

6.8 Research Involving Children

6.8.1 Policy

The special vulnerability of children makes consideration of involving them as research participants particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations apply for reviewing research involving children. The IRB may approve research involving children only if special provisions are met, the Primary Reviewer(s) must complete the Vulnerable Subjects Criteria on Reviewer Form.

The IRB may not review or make a determination regarding studies involving children, as a target population, unless it has sufficient expertise in pediatric ethical, clinical, and psychosocial issues. Therefore, a Committee member or an ad hoc member or experts who have this knowledge must be consulted by the IRB.

6.8.2 Allowable Categories

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

A. Research not involving greater than minimal risk. Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, [45 CFR§46.404]. The IRB may find that the permission of one parent is sufficient.

B. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. [45 CFR§46.405] Only if:

    a) The risk is justified by the anticipated benefit 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 permission of their parents or guardians, as set forth in 45 CFR§46.408.

C. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. [45 CFR§46.406]
    a) The risk represents a minor increase over minimal risk;
    b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those

inherent in their actual or expected medical, dental, psychological, social, or educational situations;

c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in 45 CFR§46.408.

D. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. [45 CFR§46.407]

a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

1) That the research in fact satisfies the conditions of 45 CFR§46.404-406, as applicable, or

2) The following:

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

6.8.2.1 Expert Panel

Non-Federally funded studies determined by the IRB to meet 45 CFR§46.407 for children, and meet all criteria for approval under 45 CFR§46.111, will be given a pending approval status until the research proposal is reviewed by an expert panel for recommendations as directed by the IRB. The IRB will determine the composition for the Expert Review Panel

IRB Responsibilities

The IRB shall instruct the ORA to facilitate the creation of an Expert Panel whose members represent the following:

- IRB or other neutral Facilitator;
- Between 5 and 8 Members;
- IRB Pediatric Reviewer;
- Additional IRB Representatives with appropriate clinical knowledge;
- Non-affiliated Experts in the field specific to the proposed research;
- Ethicists;
- Community Pediatricians (not involved in research, but appropriate to the study population);
- Pharmacy representatives (if applicable);
- Other applicable Experts (e.g., pediatric social worker, child psychologist, etc.); and
- IRB Community Member;
- Community Representatives that work regularly with the involved population; and/or
- Parent representatives of the target population.

The IRB will identify a deadline for completion of the panel review.

The IRB will identify questions for the panel to address and discuss and will determine the information to be provided to the panel for review. Information that may be provided may include:

- Cover letter from IRB;
- Reviewer Comment Form;
- Belmont Report;
- Regulations, including Subpart D;
- IRB Minutes;
- Complete IRB Application for Human Research including informed consent and assent documents, and the study protocol;
- Ad hoc reviewer comments (if applicable); and/or
- Summary of background information including articles, literature search, and supporting materials.

Investigator Responsibilities

- The Investigator is responsible for providing a written rationale for use of this vulnerable population, including supporting documentation (e.g., literature search) of study design, safety monitoring, and risk/benefit ratio justification.

- The Investigator will provide additional documentation or materials as requested by the IRB in order to support the justification for research under category 45 CFR§46.407.
- The Investigator will, as requested, assist the IRB in preparation for Panel and Committee review by providing any additional materials and documentation required for adequate review.
- The Investigator will be available and may be required to present the proposed study to the Expert Panel.
- The Investigator cannot initiate the research, including screening and recruitment, until all reviews (including Panel reviews) are complete and all requested revisions or recommendations are satisfied and final approval has been granted by the IRB.

Responsibilities of the Expert Review Panel

The Expert Review Panel will review the proposed research and make one of the following recommendations:

- The Expert Panel will recommend that the proposed research be disapproved, as it does not meet 45 CFR§46.404, 46.405, 46.406, or 46.407 for the protection of children as a vulnerable population;
- The Expert Panel will recommend that the proposed research meets 45 CFR§46.404, 46.405, or 46.406 for the protection of children as a vulnerable population; or
- The Expert Panel will recommend that the proposed research be approved under 45 CFR§46.407, only if the panels determine that:
  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;
  c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians as set forth in 45 CFR§46.408; and
  d. Any recommendations for revisions (e.g., added protections, etc.) for IRB review and consideration.

Following completion of the panel review, the IRB will review recommendations from the panel meetings and make a determination regarding approval of the research, including any additional study revisions identified by the Expert Review Panel.

The IRB will recommend any additional compliance guidelines (e.g., increased review frequency, observation of consent and assent process, additional DSMB protections, etc.).

6.8.3 Parental Permission, Waiver and Assent

6.8.3.1Parental Permission

As a preliminary matter, it should be noted that if the research subject is not a "child" under the Federal definition set forth at 45 CFR§46.402 (*See also* Section 6.2 of this manual), parental permission is not a requirement and consent should be sought from the research subject directly. In general, persons under 18 who are empowered by state law to make treatment decisions in certain areas of their medical care will not be considered children when making research decisions in those same areas.

In cases where the research subject is considered a child, the IRB, in accordance with 45 CFR§46.408(b), must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian, unless waiver of consent or parental permission is authorized as discussed in Section 6.8.3.2, below.

Parents or guardians from whom permission is sought must be provided with the basic elements of consent as stated in 45 CFR§46.116(a)(1-8) and any additional elements the IRB deems necessary (unless waiver of some or all of these elements is authorized by the IRB).

The IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR§46.404 or 45 CFR§46.405. The IRB's determination of whether consent must be obtained from one or both parents will be documented in the reviewer's comments in the eIRB system or on the reviewers form when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under 45 CFR§46.406and 45 CFR§46.407unless

- One parent is deceased, unknown, incompetent, or not reasonably available; or
- When only one parent has legal responsibility for the care and custody of the child.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by 45 CFR§46.117.

Waiver of Consent and Waiver of Parental Permission

6.8.3.1.1 General Waiver of Consent/Permission/Assent

The general provisions for waiver of some or all of the elements of informed consent contained in 45 CFR§46.116 applies equally to research involving children. If the requirements of that section are met, the IRB has discretion to waive parental permission and/or child assent. State law requirements concerning prospective informed consent also apply to the waiver analysis. The federal waiver requirements of Section §46.116(c) apply in very limited circumstances. Most waivers are sought under Section §46.116(d) and the requirements of this Section, are as follows:

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

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

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

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

6.8.3.1.2 Waiver of Parental Permission

In cases where the requirements for general waiver of consent pursuant to 45 CFR§46.116 cannot be met, 45 CFR 46§408(c) provides an alternate pathway permitting waiver of parental permission in some cases. Deciding whether waiver of parental permission is appropriate requires a nuanced analysis by the IRB and the principal investigator will be required to provide documentation to support that the required elements for waiver are met. In many cases, waiver of parental permission will require full board review and the IRB will involve the Lifespan Law Department as necessary. Note that the IRB may waive the requirement for obtaining parental or guardian permission under 45 CFR§46.408(c) even if the research involves more than minimal risk to the child subjects.

In order to waive parental permission and the consent requirements of Subpart A, the IRB must determine pursuant to 45 CFR§46.408(c), that the research protocol is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or

abused children), and it must determine that the following two additional criteria are put in place:

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

In deciding whether a waiver of parental permission is appropriate, the IRB may consider factors such as the following:

- Is there an argument that the research is designed to reach a group of minors who are living without parental supervision?
- Will the risk of harm or discomfort substantially increase if parental permission is required?
- Is the research conducted in a setting where the minor is already seeking support for the condition/situation that is the subject of the research, and has that setting decided that protecting the minor's confidentiality is an important goal? If so, what is the rationale for this decision?

The IRB should also consider the state law provision that requires hospitals prospectively to engage in the informed consent process with patients before enrolling them in human subjects' research. However, the assent of the child may be sufficient to meet this requirement.

6.8.3.1.3 Waiver for Emergency Research

In addition, the IRB may waive the requirement of informed consent if it finds and documents that the research meets the federal and state requirements for waiving consent because it is emergency research. *See* Section 7.6 of this Manual.

6.8.3.2 Assent from Children

Because "assent" means a child's affirmative agreement to participate in research, 45 CFR§46.402(b), the child must actively show his or her willingness to participate in the research, rather than just complying with

directions to participate and not resisting in any way. When judging whether children are capable of assent, the IRB is charged with taking into account the ages, maturity, and psychological state of the children involved.

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

The IRB presumes that children ages 8 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 8 -11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parent permission and child assent. Usually a “no” from the child overrides a “yes” from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual exceptions to these guidelines (such as when the use of an experimental treatment for a life threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents’ consent to it.

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

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this manual.

The Assent Form

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

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

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

6.8.4 Children who are Wards

The HHS regulations at 45 CFR§46, subpart D provide additional protections for children who are also wards of the State or any other agency, institution, or entity. These special protections for wards apply to two categories of research:

a. research involving greater than minimal risk approved by an IRB under 45 CFR§46.406; or
b. research with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition approved in accordance with the requirements of 45 CFR§46.407 that requires a special level of HHS review beyond that provided by the Institutional Review Board (IRB).

As set out in 45 CFR§46.409, before children who are wards of the State or any other agency, institution, or entity can be included in either of the two categories of research referenced above, the research must meet the following conditions:

a. the research must be either related to the children's status as wards; or conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards; and

b. the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

One individual may serve as advocate for more than one child, and must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research. The advocate should represent the individual child subject's interests throughout the child's participation in the research. The HHS regulations further require that the advocate not be associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

6.9 Persons with Impaired Decision Making Capacity

6.9.1 Policy

It is the responsibility of the IRB to exercise heightened scrutiny and to consider additional protections when reviewing research on subjects who suffer from medical conditions that may affect their decision-making capacity (such persons are sometimes referred to herein as "decisionally impaired"). The major concern in research involving persons who lack or may lack the capacity to give informed consent is that their disability may compromise their capacity to understand the information presented and their ability to make a reasoned decision about participation in research.

> A **decisionally impaired** person is an individual having diminished mental capacity that interferes with the ability to make sound, informed judgments regarding medical treatment or, in the research context, regarding participation in research studies. In cases where there has been no legal determination of incompetence, the assessment of whether a person is capable of making informed medical decisions requires a fact-sensitive determination that must be made, in the research context, by the investigator. More guidance on determining a person's capacity to consent is provided below.

A decisional impairment can be a temporary or permanent condition. If the impairment is temporary, the consenting investigator should, if possible, postpone the consent process until such time as the impairment has passed.

It is IRB policy that only persons who are competent (i.e., those with the capacity to provide an informed consent to participate in research) may be enrolled in a protocol, unless the investigator has explicitly requested, and the Committee has explicitly approved, enrollment of decisionally impaired persons. Special scrutiny must be given to studies designed to provoke symptoms, to withdraw subjects from therapies, to use placebo controls, and when standard therapy is withheld for all or a portion of the duration of the study.

6.9.2 Procedures

The Committee will consider for approval only those studies which meet the following requirements.

1. There must be a statement of the number of subjects as well as a careful statement of those biological or social attributes that will define their eligibility for participation in the protocol. There must be a full explanation of the rationale for including those subjects considered to be decisionally impaired. Suitable justification may include one or more of the following: (a) the purpose of the research is to develop knowledge that one can reasonably expect could benefit the class of persons that the subject represents, (b) the research is designed to study the safety and efficacy of a therapeutic modality that is likely to bring direct benefit to the individual subject, (c) preliminary studies already have been performed on less vulnerable subjects, (d) the protocol is designed to study conditions that do not affect less vulnerable populations.
2. The research presents no greater than minimal risk to the subjects, unless the research offers the prospect of direct benefit to each individual subject; or the research presents a minor increase over minimal risk and no prospect of direct benefit to the subject, but it is likely to yield important generalizable knowledge about the subject's disorder or condition. Minimal risk means "that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." A minor increase over minimal risk may exist when the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situation. The IRB must decide what level of risk constitutes a minor increment over minimal; generally such risks would pose no significant threat to the subject's health or well-being.

3. Prior to enrollment of persons with questionable capacity to give an informed consent, the investigator must determine whether the subject is competent to give informed consent to participate. Competence may be defined as an ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to express a choice. For more detailed guidance on determining capacity to consent, please refer to the RIH or TMH policy on medical-decision-making.

Additionally, the investigator must clearly specify to the IRB how competency will be assessed when there is a question of diminished capacity to consent. As part of positive competence assessment, participants may be required to respond accurately to a set of questions that demonstrate understanding of critical aspects of consent for the particular study (these questions would be free response, and approved by the IRB, if necessary). In some cases, the investigator may find a psychiatric consult useful to assess a patient's competency, but such a consult is not required unless specifically required by the IRB.

For research protocols involving subjects who have fluctuating or limited decision making capacity, the IRB should consider requiring that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should also be considered in some cases. Per the IRB's discretion, third party consent monitors might be used during the recruitment and consenting process, or waiting periods might be required to allow more time for the subject to consider the information that has been presented.

4. The specific basis for Committee approval of research involving persons who are incapable of giving informed consent must be adequately documented in the minutes. Subjects who are judged to be decisionally impaired may have a court-appointed legal guardian, and this person may be approached to consent on the ward's behalf. Some individuals may be decisionally impaired and have no legal guardian; for example, a patient with Alzheimer's disease may be cared for by someone who is not the legal guardian or even next-of-kin. The investigator must indicate the status of those subjects who will be enrolled so that the IRB may determine the necessary procedures for obtaining consent. If a legal guardian or next-of-kin must participate in the consent process, the consent form must be adapted for their signatures. The investigator must document that the individual giving surrogate consent on behalf of the incompetent patient is eligible to do so under the applicable Lifespan medical decision-making policy.

6.9.3 IRB Composition

If deemed necessary by the IRB, on a case-by-case basis, consideration shall be given to inclusion in the committee of one or more individuals who are knowledgeable about and experienced in working with decisionally impaired subjects.

6.9.4 Surrogate Consent

HHS regulations stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative ("LAR").[1] Furthermore, HHS regulations define a LAR 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.[2] Federal law provides no further guidance on LARs and thus defers to state law.

6.9.4.1 Rhode Island Law

The right of a surrogate to make medical decisions on behalf of an incapacitated patient is well grounded in Rhode Island law. The law concerning Rights for Persons with Developmental Disabilities provides that "participants" covered by the chapter have the right "to participate in the development of [an] individualized plan of care and to provide informed consent to its implementation or to have an advocate provide informed consent if the participant is not competent to do so."[3] The term advocate is defined as "(i) a legal guardian; or (ii) an individual acting on behalf of a person with a developmental disability in a manner clearly consistent with the interests of the person with a developmental disability and includes a family member, friend, or professional advocate."[4] Under the chapter, advocates also explicitly have the right to consent on behalf of the incompetent person to the administration of "behavior modifying" treatment, such as psychotropic drugs.[5]

Rhode Island also recognizes the right of surrogate decision-makers to make end of life decisions on behalf of incompetent persons. In the seminal case, *Gray v. Romeo*,[6] the husband of a woman in a persistent vegetative state was allowed to act as a surrogate decision-maker in deciding to withdraw a feeding tube and life support from his wife, and thus to precipitate her death. The court based its decision on clear evidence supporting a finding that the wife, if competent, would have exercised her right to refuse life sustaining medical treatment.[7]

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[1] *See* 45 CFR 46.116.
[2] *See* 45 CFR 102(c).
[3] RIGL Section 40.1-26-3.
[4] **Section 40.1-26-2(1).**
[5] *See* Section 40.1-26-3(6)
[6] 697 F. Supp. 580 (D.R.I. 1988).
[7] *Id.* at 587.

In the ethical literature on consent to treatment, plans of care involving "behavior modifying" treatment or withdrawal of life-sustaining care are often referred to as extra-ordinary care, versus ordinary or routine care. Where extra-ordinary care is involved, a higher standard of care is often applied when determining whether surrogate consent is permissible, and who the surrogate decision-maker should be. Surrogate consent to participation in research is analogous to surrogate consent to extra-ordinary care; in both cases, the assessment of the incompetent person's best interest is complex, and the surrogate decision-maker carries a heightened burden in exercising substituted judgment on behalf of the incompetent person. The fact that Rhode Island law permits surrogates to consent on behalf of decisionally impaired patients in extra-ordinary care situations supports the practice of permitting surrogate consent in the research context.

Even more to the point, the Rhode Island Health Care Power of Attorney Act[8] allows a competent person to appoint a surrogate or agent with broad authority to make medical decisions, including decisions about research participation, on behalf of the person in the event of incapacity. In order to appoint an agent, the person must execute a statutory form of durable power of attorney (the "Power of Attorney Form" or the "Form").[9] The statute provides that the agent's decision-making power is not bound by law, but only by the best interests of the incompetent person, as explicitly expressed in the Form or as otherwise made known: "The agent must act consistent with your desires as stated in this document or otherwise known. Your agent must act in your best interest. Your agent stands in your place and can make any health care decision you have the right to make."[10] In an effort to prompt the executor of the Form to consider fully the role of the agent, and to build any desired limitations into the Form, the Form lists out examples of the types of decisions an agent is permitted to make. The agent's ability to consent to research is highlighted: "Whenever I can no longer make decisions about my medical treatment, my health care agent has the power to . . . make decisions concerning participation in research."[11] Thus, unless a Form specifically prevents the agent from making decisions related to participation in research, this type of decision-making is allowed on behalf of the incapacitated person.

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[8] RIGL Chapter 23-4.10

[9] The Rhode Island Attorney General (RIAG)'s office published a new form of durable power of attorney in January, 2003 under the heading "Rhode Island Durable Power of Attorney for Health Care: An Advance Care Directive" (*hereinafter,* "Power of Attorney Form" or "Form"). Though this Form has not yet been codified, it is the intention of the RIAG that it be used by persons wishing to appoint a health care agent. *See also* RIGL Section 23-4.10-2 (Statutory Form of Durable Power of Attorney).

[10] *See* Form.

[11] *See id*.

The research provision in the Power of Attorney Form functions to invest the incapacitated person with the personal autonomy he or she would have had if competent to make medical decisions, including decisions about whether to participate in research.[12] An appropriately chosen surrogate, acting in the best interest of the subject, in accordance with the subject's known belief system, and preferably in accordance with the subject's previously expressed wishes, stands in the subject's stead when exercising the right to consent or not consent to participation in research.

6.9.4.2 Hospital Policy

The statement in the Power of Attorney Form concerning research provides the legal cornerstone for the IRB's policy on surrogate consent to research. Though not all potential research subjects who are incompetent will have appointed health care agents, the fact that agents are legally allowed to consent to research indicates that, under appropriate circumstances, other surrogates could make such decisions as well.

As stated earlier, it is the policy of the IRB to allow surrogate consent to research only in cases where the study itself has been approved under the IRB's Decisionally Impaired Policy and when an appropriate surrogate can be identified. In general, the Decisionally Impaired Policy functions to prompt the IRB to consider the research design and to evaluate from a scientific, ethical and legal perspective whether, on balance, the study is in the best interest of the subject. In practice, application of the Policy protects the best interests of the subject by preventing enrollment of incompetent subjects in research involving more than minimal risk, except where there is a strong countervailing prospect of direct benefit to all of the subjects. Reaching a conclusion about whether a study poses minimal risk or is therapeutic as applied to all subjects often involves detailed review and discussion led by knowledgeable members of the committee. Therefore, the full IRB is encouraged to convene sub-committees when it is unsure about the application of the Policy to a particular protocol.

[12] RIGL 23-17-19.1(10) provides: "If the health care facility proposes to use the patient in any human experimentation project, it shall first thoroughly inform the patient of the proposal and offer the patient the right to refuse to participate in the project." Our office reads this provision as consistent with the research provision of the Power of Attorney Form in that the Form creates a mechanism for persons to exercise their autonomy in the medical arena, including research, even after they become incapacitated.

The IRB's role in protecting the research subject is similar to the surrogate decision-maker's charge under Rhode Island law to apply the best interest standard. Thus, the IRB's approach requires a double application of the best interest standard. First, the IRB must decide that the research design itself is consistent with the subject's best interest; then, the surrogate decision-maker must decide, with the best interest of the subject in mind, whether the subject, if competent, would have chosen to participate in the research. This process is consistent with the spirit of Rhode Island law, and it provides heightened protection for the incompetent subject.

As described above, the process of selecting the appropriate surrogate decision-maker in the research context is governed by the relevant hospital's policy on medical decision-making. In the case of persons younger than eighteen (18), generally the parent is the only appropriate surrogate (some exceptions do apply). For adult patients or subjects, state law and the applicable policy provide that, when a close family member cannot be located to serve as the surrogate, the attending physician or investigator can look to a friend or more attenuated family member with a clear connection to the person to make decisions. In the research context, however, it is also appropriate for the principal investigator charged with identifying the surrogate decision-maker to approach potential surrogates skeptically and to exercise heightened care to ensure that the chosen surrogate possesses the requisite information and connection to make a substituted judgment on behalf of the potential research subject. In practice, this could mean that the principal investigator would limit the search for a surrogate to immediate family members in most cases, though this is not required.

Finally, the principal investigator, and indeed all clinicians, must be reminded that even when surrogate consent is appropriately obtained, it is never appropriate to administer procedures against the will of the incapacitated person. Thus, if a subject exhibits an unwillingness to participate in research that is more than just reflexive behavior, the research should be stopped even if the study has been approved by the IRB and surrogate consent has been appropriately obtained.

6.9.5 Changes in Decision Making Capacity

In the event research participants become incompetent or impaired in decision making capacity after enrollment, the PI is responsible for notifying the IRB and Research office. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research participants.

6.9.6 Emergency Waiver of Informed Consent

On a case-by-case basis, the Institution is willing to consider whether "Emergency Waiver of Informed Consent" for decisionally impaired patients for whom no surrogate decision-maker is available is appropriate and consistent with Federal and State law and hospital policy. Please refer to Section 7.6.2 of this manual and prospectively contact the Lifespan Office of Research Administration if a question of this sort arises.

7 Investigational Drugs & Devices in Research

7.1 Policy

Clinical trials using an investigational drug or device or conducted under the auspices of a Lifespan Affiliate require prospective review and approval by the IRB. The use of an unapproved investigational drug, device, agent, and/or biologic, requires an FDA investigational new drug application (IND) or an investigational device exemption (IDE).

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

7.2 Definitions

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

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

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

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

Emergency Use. Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

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

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

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

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

7.3 FDA Exemptions

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

1. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

7.4 IND/IDE Requirements

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

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

1. Industry sponsored protocol with IND/IDE.
2. Letter from FDA.
3. Letter from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study device as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study device is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

1. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
2. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

7.4.1 IND Exemption

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

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a 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 [21 CFR§56 and §50, respectively];
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR§312.7];
7. The research does not intend to invoke 21 CFR§50.24 (Exception from informed consent requirements for emergency research).

Note: The following are also exempt from the IND requirements : (a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and (b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR§312.160 .

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

1. It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
2. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
3. It is shipped in compliance with §312.160

7.4.2 Exempted IDE Investigations

For devices, an IDE may not be necessary if:

1. 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 ;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR§807 in determining substantial equivalence;
3. 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;
4. 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;
5. The research involves a device intended solely for veterinary use;

6. The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR §812.5(c);
7. 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.

7.5 Responsibilities

7.5.1 Investigator Responsibilities

1. The investigator is responsible for ensuring that the research is conducted according to all regulatory guidelines and must obtain approval from the Lifespan IRB.
2. The test article must be used only in accordance with the plan of investigation as described in the FDA-approved IND/IDE application (if appropriate) and the IRB- approved protocol; and the investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol GCP ***2.12***.
3. The test article may only be used in participants under the Principal Investigator's personal supervision or under the supervision of physicians who are directly responsible to the Investigator; and the informed consent from the participant or the participant's legally authorized representative is prospectively obtained, unless a waiver of consent has been approved by the IRB for emergency use or emergency research.
4. Informed consent must meet the requirements outlined in the IRB Informed Consent policies and procedures
5. No claims are to made which state or imply, directly or indirectly, that the investigational test article is safe or effective for the purposes under investigation or that the drug is in any way superior to another drug;
6. The informed consent document must contain a statement that the test article is "investigational, meaning non-FDA approved";
7. The informed consent document must contain a statement that the FDA may have access to the participant's medical records as they pertain to the study; and
8. The Investigator must assure that throughout the consenting process and study participation the participant understands that the investigational test article is under investigation, and that its benefits for the condition under study are unproven.

9. For Phase I studies, the informed consent document must disclose that the purpose of the research includes examining the drug's safety. For Phase II and Phase III studies, the informed consent document must disclose that the purpose of the research includes examining the drug's safety and efficacy (effectiveness).

10. The investigator is responsible for the investigational drug/device accountability which includes storage, security, dispensing, administration, return, disposition and records of accountability).

    Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator. ***GCP 4.6.2***

11. The investigator proposing the drug/device research will be required to provide a plan that will be evaluated by the IRB that will include: (a) Storage, (b) Security, (c) Dispensing.

    The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants. ***GCP 4.6.3.***

    Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

12. For research involving investigational new drugs where pharmacy will be responsible for storing and dispensing the drug:
    a. The PI is responsible for informing Pharmacy Service that IRB approval has been obtained.
    b. The investigator is responsible for informing Pharmacy when a subject has withdrawn consent or if treatment has been suspended or terminated for any reason.
    c. The PI must inform the Pharmacy Service when a study involving investigational drugs has been terminated.

13. If an investigational drug/device is not stored in the pharmacy, the investigator is responsible for the storage, security and dispensing of the drug/device. All drugs/devices received for a study must be

stored in a locked environment under secure control with limited access. The area must be within an area of investigator's control. A log must be kept regarding the receipt, use and/or dispensing of the drug/device and the disposition of remaining drug/devices at the conclusion of the investigation.

14. For research involving investigational devices:
    a. If a device considered NSR by the investigator or sponsor, is determined to have significant risk upon IRB review, the investigator is responsible for notifying the sponsor of the IRB's determination upon receipt of written notice. The PI should provide the IRB with confirmation of this action.
    b. The investigator shall submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect.
15. The investigator shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures in Section 8.
16. When a PI holds the IND or IDE, he/she is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the Guidance on Requirements for the Investigator as a Sponsor and will comply with the regulatory responsibilities of a sponsor. The RPO will conduct education programs for investigators holding an IND or IDE on the sponsor regulations.

7.5.2 IRB Responsibilities

- The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR§56.111).
- For research involving investigational devices:
    - Unless the FDA has already made a risk determination for the study, the IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE

application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as NSR is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.
- The IRB will not review protocols involving significant risk devices under expedited review.
- The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.
- If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

7.5.2.1 SR/NSR Determination

The Investigational Device Exemption (IDE) regulations (21 CFR§812) describe two types of devices, Significant risk (SR) devices and Non-significant risk (NSR) devices. The SR devices are governed by 21 CFR §812. NSR devices are governed by abbreviated 21 CFR§812 and that is §812.2(b). IRB approval for both SR and NSR studies is required. For NSR devices, however, the IRB serves, or can serve, as the FDA surrogate with respect to review and approval of NSR studies. IRBs are not required to report NSR studies to the FDA nor are the sponsors.

The IRB first needs to make the determination of SR vs. NSR. The IRB does not have to agree with the sponsor with regards to this determination. If the IRB feels it necessary they can consult with the FDA or request the sponsor consult with the FDA in making this determination. If the IRB determines the device to be a SR device then the study may not be approved until the FDA approves the investigation and issues an IDE. If the IRB determines the study to be NSR then they can approve the study, and this in essence becomes the IDE, and the study may proceed.

The sponsor however has more of a role in this then providing their determination of NSR. They need to provide the IRB with the risk assessment and rationale they used in making their determination of NSR, 21CFR§812.150(b) (10). This information may include:

- Their initial assessment of the device and why they determined it to be NSR
- A description of the device, its use and method of operation
- Any reports from prior investigations, i.e. European trials, etc.
- A description of patient selection criteria
- Monitoring procedures

- Any other IRBs determinations regarding SR vs. NSR
- And any other information the IRB may ask for in making its determination.

The IRB makes its determination on how the device will be used in this particular study and not on how the device itself functions. The determination is based on whether or not the device, as used in this particular study, could result in a life-threatening situation or necessitate medical or surgical intervention to preclude such a situation.

The sponsor should provide the information as outlined above. The submission to the IRB of how the device functions is important but more information is required. Information from other studies that have been conducted should be provided for review.

The IRB may ask the sponsor to seek FDA advice for this determination or the IRB can seek FDA advice in making its determination. The manufacturer of this device in the end will still need to go to the FDA prior to marketing. This is only with regards to clinical trials. The IRB makes no determination regarding once the trial is over the product is ready for marketing.

The manufacturer is accountable to the FDA in presenting data regarding:

- good manufacturing practices (GMP),
- data to support their marketing claims,
- Believe there are enough predicate devices already approved that would allow them to submit under a 510K and not a PMA, etc.

For additional information or for questions regarding NSR devices contact the Research Protections Office.

The IRB will make the determination of NSR if applicable based on the information provided and an agreed rationale. The determination and rationale will be voted upon and reflected in the meeting minutes. If the same device is used in another study the IRB will need to make a determination of NSR for each new study based on the information provided for that study.

7.6 Emergency Use

7.6.1 Emergency Use Exemption from Prospective IRB Approval.

HHS regulations do not permit human subjects research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval,

the patient may not be considered a research subject under 45 CFR§46. However, nothing in the HHS regulations at 45 CFR§46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State or local law.

The Emergency Use exception defined here applies only to situations where the patient or the patient's surrogate is able to give consent to the proposed medical intervention (verbal-witnessed and documented in the patient record). If it is not possible to get consent, the intervention is not permitted unless another exception (see below) applies.

In cases where a clinician wishes to offer a patient a test article regulated by the FDA on an emergent basis in a life threatening situation without prior IRB review, the following criteria must be true:

- The subject is in a life-threatening or severely debilitating situation.
- No standard acceptable treatment is available.
- There is not sufficient time to obtain IRB approval.
- The use is reported to the IRB within five working days.
    - Any subsequent use of the test article is subject to IRB review.
    - Consent will be obtained in accordance with FDA regulations, or the circumstances meet the exception to the requirement for consent in FDA regulations.
    - Under FDA regulations, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a subject, and the FDA may require data from an emergency use to be reported in a marketing application.

If the research involves an investigational drug, and the FDA has issued an IND one of the following is true:

- Informed consent is sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 21 CFR§50 and informed consent is appropriately documented in writing using the long or short form of consent documentation, in accordance with and to the extent required by 21 CFR§50.27.
- Informed consent is not required because all of the following are true:
    - Before the use of the test article both the investigator and a physician who is not otherwise participating in the clinical investigation certified in writing that:
        - The subject is confronted by a life-threatening situation necessitating the use of the test article.

        - Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
        - Time if not sufficient to obtain consent from the subject's legal representative.
        - There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the participant.
    - The above written certification is submitted to the IRB within five working days after the use of the test article.
- Informed consent is not required because all of the following are true:
    - Immediate use of the test article is, in the investigator's opinion, required to preserve the life of the participant.
    - Time is not sufficient to obtain the independent determination a physician who is not otherwise participating in the clinical investigation.
    - Before the use of the test article the investigator will certify in writing all of the following:

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

    - After the use of the test article a physician who is not otherwise participating in the clinical investigation will certify in writing within five working days after the use of the article all of the following:
        - The subject is confronted by a life-threatening situation necessitating the use of the test article.
        - Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
        - Time is not sufficient to obtain consent from the subject's legal representative.
        - There is available no alternative method of approved or generally recognized therapy that provides an

equal or greater likelihood of saving the life of the subject.

- The above written certification will be submitted to the IRB within five working days after the use of the test article.

If the PI notified the IRB prior to the emergency use of an investigational test article, the circumstances will be reviewed by the Director of the Research Protection Office (RPO) to determine that it meets FDA regulations and the investigator will be advised accordingly. All after-the-fact reports to the IRB of emergency use will be reviewed by the Director of the RPO and the IRB Chairperson to determine whether the action taken under the circumstances was in compliance with FDA regulations. The full IRB will be notified on the next agenda of all such reports.

If the emergency intervention does not involve a test article regulated by the FDA (for example, in the case of an experimental surgical technique not involving an FDA regulated test article), no follow up with the IRB is needed since such intervention would be considered medical treatment and not research. However, such intervention would be governed by other applicable Lifespan policies and applicable state and Federal laws. Any questions should be directed to the Lifespan Risk Management Department or the Office of the General Counsel.

7.6.2 Emergency Waiver of Informed Consent

Situations may arise where a clinician wishes to offer a patient an emergency intervention involving either an FDA regulated test article, or a non-FDA regulated intervention being evaluated pursuant to a research protocol approved at Lifespan, when neither the patient nor the patient's surrogate is available to consent to such intervention. If the situation involves "Planned Emergency Research", as discussed below, one set of rules applies. **In all other cases where emergency waiver of informed consent is sought, the clinician must prospectively contact the RPO, which Office will involve the Lifespan Risk Management Department or the Office of the General Counsel as needed.**

Certain exceptions may be available in state and federal law to allow such waiver of informed consent; however, these laws are very complex and must be navigated with extreme care. Without limitation, relevant laws that should be considered are: 21 CFR§50.23 (FDA exception for waiver of informed consent if certain, very specific, certifications can be made by PI and independent physician) and RIGL 23-17-19.1(10) (relevant to planned emergency research). Section 6.9 of this Manual governing Persons with Impaired Decision-Making Capacity need also be considered.

As an overriding principle, this route should only be considered if NO ALTERNATIVE METHOD OF APPROVED OR GENERALLY RECOGNIZED THERAPY IS AVAILABLE THAT PROVIDES AN EQUAL OR GREATER LIKELIHOOD OF SAVING THE PATIENT'S LIFE.

7.6.3 Expanded Access of Investigational Drugs

FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:

1. Compassionate Use: The term "compassionate use" is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.
2. Group C Treatment Investigational New Drug (IND): A means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, Lifespan IRB requires prospective IRB review and approval.
3. Open – Label Protocol: A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.
4. Parallel Track: A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that "parallel" the controlled clinical trials and are essential to establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a protocol-by-protocol basis, waive the provisions of 45 CFR§46 where adequate protections are provided

through other mechanisms, prospective IRB review and approval is required by the Lifespan IRB.

5. Treatment IND or Biologics: A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Prospective IRB review and approval is required.

    a. There are four requirements that must be met before a treatment IND can be issued:

        i. The drug is intended to treat a serious or immediately life-threatening disease;

        ii. There is no satisfactory alternative treatment available;

        iii. The drug is already under investigation or trials have been completed; and

        iv. The trial sponsor is actively pursuing marketing approval.

    b. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:

        i. Informed Consent. Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, the IRB should ensure that potential subjects are fully aware of the risks involved in participation.

        ii. Charging for Treatment INDs. The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee should pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. Charging for

participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

6. Single-Patient Use: The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required (See 5 above).
7. Emergency IND: The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics.

7.6.4 Emergency Waiver of IND

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

7.6.5 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR§50.24 for FDA regulated research and by the waiver articulated by HHS at 61 FR 51531-33 for non-FDA regulated research. Among other requirements, the research plan must be

carried out under an approved IND or IDE, if applicable, must be approved in advance by the IRB, and publicly disclosed to the community in which the research will be conducted. The applicable state law permitting such research to occur is found at RIGL 23-17-19.1(1)). The waiver of informed consent is inapplicable to research involving children (subpart D), fetuses, pregnant women and human in vitro fertilization (subpart B) and research involving prisoners (subpart C).

Research that proceeds according to this pathway is subject to prospective IRB approval, as opposed to Emergency Use research approved pursuant to 21 CFR§56.104(c).

7.6.5.1 Planned Emergency Research

The FDA exception from informed consent requirements for emergency research under FDA regulations, *21 CFR§50.24,* permits planned research in an emergency setting when human subjects (participants) who are in need of emergency medical intervention cannot provide legally effective informed consent and their legally authorized representatives (LARs) are unable to give informed consent as well.

The Secretary of Health and Human Services (HHS) has implemented an Emergency Research Consent Waiver under *45 CFR§46.101(i)* with provisions identical to those of the FDA with the exception of the IND/IDE requirement and the definition of family member includes spouses of brother/sisters. The waiver is not applicable to research involving prisoners, see *45 CFR§46.101(i) & §46.306(b).*

Additional state requirements apply as well.

Most planned emergency research involves the use of an FDA regulated test article and therefore is subject to FDA regulations as listed above. The Research Protection Office recommends Principal Investigators who are planning emergency research contact the Director of the Research Protection Office for assistance at least 4-5 months prior to the planned start date. The requirements are very complex and include consultation within the institution, in the community in which the research is to be conducted, the FDA, and the Department of Health and Human Services (DHHS).

These Emergency Research policies and procedures apply to Planned Emergency Research. Planned Emergency Research is different from Emergency Single Time Use of a Test Article as regulated under FDA *21 CFR§56.104(c).*

7.6.5.2 Definition

Planned Emergency Research-Research that involves participants (subjects) who, because of their condition (e.g., unconsciousness) are in a life-threatening situation that makes intervention necessary, are unable to give informed consent, and to be effective, the intervention must need to be administered before obtaining informed consent from the subject's legally authorized representative is reasonably possible.

7.6.5.3 Policy/Procedures

The IRB that initially reviews and approves the planned emergency research may approve the study without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB Committee (that includes a member who is a licensed physician and who is not otherwise participating in the clinical trial) finds that the following criteria from FDA 21 CFR§50.2 have been met:

1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of

subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) (a) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

> (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
>
> (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
>
> (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
>
> (iv)Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
>
> (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family

members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with §56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under §312.30 or §812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other

IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

7.6.5.4 Community Consultation

Community Consultation is an extremely important requirement for conducting planned emergency research. The community in which the research is to take place and the persons that would likely be affected by the research must be informed and must agree that it is acceptable to begin the planned emergency research. Consultation with the community must be conducted prior to full approval by the IRB.

Depending on the nature of the research, community consultation may consist of any of the following activities:

Survey (s);

Questionnaire (s),

Focus groups and

Community meetings.

The content of these activities/meetings must be reviewed and agreed upon prior to conducting the consultations by the IRB chair or designee and the Director of the RPO.

In order to facilitate educating, informing and publicly disclosing the plans for the investigation and its risks and expected benefits to the community in which the clinical investigation will be conducted; and, from which the subjects will be drawn, every effort must be made to engage a representative sampling of persons or organizations in the affected community consultation process to obtain their input and agreement that the research should go forward. The IRB cannot approve Planned Emergency Research without this part of the process being completed in a thorough manner. All community meetings should include the Principal Investigator, and may also include a representative from the Research Protection Office, and where appropriate, a member of the IRB. Upon completion of the community consultation process, the PI must present a written report to the IRB citing any and all issues raised through the process and conclusions. The IRB will determine if there is community support based on the report.

The PI is expected to keep and maintain detailed documentation that all of the above required procedures for planned emergency research and

emergency waiver of consent are met. The documentation should be included in the submission to the IRB for full approval.

All protocols that the IRB approves pursuant to this emergency research exception shall be filed with the Rhode Island Department of Health, where they will be made publicly available.

7.7 Humanitarian Use Devices (HUD)

Federal Regulations allow the use of a device that is 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. The Food and Drug Administration, FDA, issues a Humanitarian Use Device Exemption, (HDE,) to use an HUD in clinical treatment or as the subject of a clinical investigation.

7.7.1 Physician or Health Care Responsibilities for the Use of a HUD

The physician or health care provider may utilize the HUD when agreeing to the following:

- Only the holder of the HUD agreement with the FDA must use the HUD
- The physician or health care provider must utilize the HUD for treatment, diagnosis, or research in accordance with the labeling of the device, intended purpose, and in the designated population for which the FDA approved its use;
- The physician or health care provider must inform the patient that the HUD is a device authorized under Federal law for use; however, the effectiveness of the device for a specific indication has not been demonstrated; and
- The physician or health care provider will obtain informed consent when the use of the HUD involves research or when required by the IRB.

7.7.2 IRB Submission Requirements for Use of an HUD

The use of a HUD does not constitute research unless the physician or health care provider intends to collect data from its use. **Regardless of the intended use, a HUD requires prospective IRB review and approval.**

The physician must submit an application to the IRB for review at a convened meeting. In addition, the Investigator must include the following information:

- The generic and trade name of the device;

- The FDA HDE number
- Provide a letter from the Sponsor or FDA, if applicable, to verify HDE number and permission for use
- The date of HUD designation;
- The indications for use of the device;
- A description of the device;
- Contradictions, warning, and precautions for use of the device;
- Adverse effects of the device on health;
- Alternative practices and procedures;
- The HUD brochure;
- Marketing history; and
- A summary of studies using the device.
- Include any information, that will be provided to patients i.e. patient info booklet

The IRB approval must verify that the use of the HUD, as proposed, is congruent with current labeling of the device and does not exceed the scope of the FDA approved indication.

The IRB may impose more stringent restrictions for use of the HUD as a means of additional protections, as deemed necessary.

The initial review of an HUD is to be completed by the full IRB Committee. The full Committee may make the determination at initial review that subsequent continuing reviews may be conducted by expedited review.

7.7.3 Considerations for Prompt Reporting.

Whenever the physician or health care provider receives or otherwise becomes aware of information, from any source, that reasonably suggests that a HUD has or may have caused or contributed to the death or serious injury of a patient, the physician or health care provider must report such findings to the FDA and the IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect or problem. This reporting is in addition to, not a substitute for, FDA and/or manufacturer reporting requirements in accordance with 21 CFR§803.30. The physician or health care provider shall promptly report any FDA action(s) regarding the HUD to the IRB.
Modifications to the HUD or the clinical use of the HUD are to be promptly reported to the IRB in accordance with the IRB policy for amendments.

8 Unanticipated Problems Involving Risks to Subjects

8.1 Policy

Federal regulations require organizations to have written policies and procedures to ensure the prompt reporting of unanticipated problems involving risks to subjects or others to the IRB, appropriate institutional officials, and regulatory agencies. (NOTE: For simplicity, unanticipated problems involving risks to subjects or others will be referred to as "unanticipated problems" in this policy).

Not all unanticipated problems involve direct harm to subjects. Events can occur which are unexpected and result in new circumstances that increase the risk of harm to subjects without directly harming them. In addition, the event may have presented unanticipated risks to others (e.g., the sexual partners of the subjects, individuals the subject may come in contact with, family members, research personnel, etc.) in addition to the subjects. In each case, while the event may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported.

Events in which there is direct harm to subjects are referred to as "Adverse Events". Although adverse events occur most commonly in the context of biomedical research, adverse events can occur in the context of social and behavioral research.

Only unanticipated problems or unexpected adverse events that are related to the research, and place subjects or others at a **greater risk of harm** need be reported. Other unanticipated problems/adverse events that do not meet these reporting criteria do not need to be reported to the IRB. However, if the sponsor requires the investigator report to their local IRB all events that occurred on the study approved through the Lifespan IRB the use of the sponsor required but otherwise not reportable form (AE3) will facilitate this reporting.

These procedures describe how unanticipated problems are reported to the Lifespan IRB.

The phrase unanticipated problems involving risks to subjects or others is found but not defined in the HHS regulations at 45 CFR§46.

8.2 Definitions

OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

Unanticipated problems

(1) unexpected (in terms of nature, severity, or frequency) given

- the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
- the characteristics of the subject population being studied;

(2) related or possibly related to participation in the research (in the OHRP guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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

Adverse Event - HHS regulations at 45 CFR§46 do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities. In the OHRP guidance document, the term *adverse event* in general is used very broadly and includes any event meeting the following definition:

> 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Serious Adverse Event – An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. (21CFR 312.32**)**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience **when**, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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.

Unexpected Adverse Event - Any adverse 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. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Related - For this policy an event is “possibly related,” there is a reasonable possibility that the event is more likely than not to have been caused by the research article or procedure. In general, adverse events that are determined to be at least partially caused by the research article or procedure would be considered related to participation in the research

Substantive Action - An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

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

8.3 What Unanticipated Problems NEED to be reported to the IRB?

Reportable (to the IRB) Unanticipated Problems/Adverse Events–
HHS states adverse events only need to be reported to the IRB if they are unanticipated, serious, related to the research, and places subjects or others at **GREATER RISKS** than was previously known or recognized. These events routinely warrant substantive changes in the research protocol or informed consent document/process OR other corrective actions in order to protect the safety, welfare, or rights of subjects.

FDA states adverse events need be reported to the IRB only if they were unexpected, serious, and would have an implication for the conduct of the study (e.g., requiring a significant and usually safety-related, change in the protocol, informed consent or investigator's brochure).
Possible exceptions to this FDA determination would include situations in which the specificity or severity of the event is not consistent with the description in the IB, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.
The FDA lists several exceptions to the single occurrence reporting requirements such as:

- An event that is uncommon and strongly associated with drug exposure
- An event not commonly associated with drug exposure but uncommon in the study population
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem
- An AE addressed in the IB, Protocol or ICD but occurs at a specificity or severity that is inconsistent with prior observations.

8.3.1 What Adverse Events need to be reported to the IRB?

Local Adverse Events: The investigator must evaluate the event based on the information provided above, is the event unanticipated, serious, related to the research, and places subjects or others at **GREATER RISKS** than was previously known or recognized? If yes than this would need to be reported to the IRB. These events routinely warrants substantive changes in the research protocol or informed consent document/process OR other corrective actions in order to protect the safety, welfare, or rights of subjects. FDA states adverse events need be reported to the IRB only if they were unexpected, serious, and would have an implication for the conduct of the study (e.g., requiring a significant and usually safety-related, change in the protocol, informed consent or investigator's brochure).

The investigator must follow all reporting requirements as outlined by their sponsor and monitoring board/plan. If the investigator determines this event is reportable the report should be submitted within 10 working days of becoming aware of the event. If the investigator determines the local event is not reportable but the sponsor or the DSMB later determines the event to be reportable the investigator must submit a report indicating this change in reportability.

ALL Local fatalities, occurring with subjects on Active Treatment whether related or unrelated, must be reported to the IRB within 24 hours of the investigator becoming aware of the event. This 24 hour notification may be via

phone, fax, email or report form and should be followed by a written report as soon as possible. Any (related) local fatality must be reported to the sponsor and the FDA, if applicable.

Other Site Adverse Events: The local investigator need only report external adverse events to their local IRB when the report meets the reportable criteria as outlined above and are accompanied with (1) a reason why this report meets the reportable criteria; and (2) a description of any proposed changes or other corrective actions to be taken by the investigators in response to the unanticipated problem. **If no action or changes to the study are required then according to both HHS and FDA these events need not be reported to the local IRB.**

Reportable (to the IRB) Unanticipated Problems not Adverse Events - Events that were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects or others (e.g. loss of a laptop with participant information).

Examples of Adverse Events that Do Not Represent Unanticipated Problems and DO NOT Need to be Reported under the HHS Regulations at 45 CFR§46

(1) A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that the there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers – in terms of nature, severity, and frequency – was expected.

(2) An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved

protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR§46

(1) A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo- controlled, double-blind, and phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the subject's acute renal failure was (a) unexpected in nature, (b) related to participation in the research, and (c) serious.

(2) A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia. Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

(3) Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug.

At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.

(4) A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In all of these examples, the adverse events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

Examples of Unanticipated Problems that Do Not Involve Adverse Events and <u>Need to be Reported</u> Under the HHS Regulations at 45 CFR§46

(1) An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

(2) As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

(3) Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an unanticipated problem that must be reported because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these examples, the unanticipated problems warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting

agency head and OHRP in accordance with HHS regulations at 45 CFR§46.103(a) and §46.103(b)(5).

8.4 Reporting Procedures

The principal investigator must promptly report unanticipated problems to the IRB. Those unanticipated problems that are reportable to the Lifespan IRB by the investigator are:

a. An unanticipated problem that is not an adverse event.
b. An unanticipated event related to the research that exposes individual research participants or others to GREATER risk of physical or psychological harm than was previously known. (Others can include investigators, research assistants, students, the public, etc.).
c. Interim DSMB or Monitoring reports indicating non-compliance or other issues that could increase risk to subjects or others
d, Publications or new information that indicates an increase or change in the risk/benefit ratio
e. Warnings from the FDA or changes in FDA labeling or withdrawal of a marketed drug/device/biologic used in the study
f. Suspension of the study or investigator by the sponsor or regulatory agency
g. Certain protocol deviations **(see below)**
h. Complaints from subjects that indicate a previously unrecognized risk related to the study
i. Incarceration of a participant in a protocol not approved to enroll prisoners who remains actively involved in the research protocol.
j. Breach of Confidentiality (e.g. loss of a laptop containing identifiable research data; transmittal of unencrypted study data)
k. Any other problems/events that impact the risk/benefit ratio of the study

Certain Protocol Deviations might be unanticipated problems and are reportable to the IRB. Investigators must promptly report protocol deviations to the Lifespan IRB if the deviation was a **major deviation from the protocol that adversely affected the rights and welfare of the subjects, the safety of the subjects, the integrity of the study data and/or the subject's willingness or ability to continue study participation**.

Major protocol deviations are:

1. Intentional deviations to eliminate an immediate hazard
2. Enrollment deviations
3. Consent deviations (signing an outdated informed consent that has had revisions since that version was approved which added risks; not signing an informed consent).

4. Procedural deviations that may have resulted in an increase risk to the subjects or others (dosing error; missed evaluation being used to assess subject safety or eligibility).
5. Protocol deviation (accidental or unintentional change to the IRB approved protocol without prior IRB approval) that harmed participants or others or that indicates participants or others may be at increased risk of harm.

8.4.1 Reporting

Reporting Timeframe (only reportable unanticipated problems/events have a reporting timeframe)

Local AEs. The investigator should assess whether the local adverse event represents an unanticipated problem following the guidelines described in Section 8.3 above. The reportable criteria above, unexpected or unanticipated, serious, places subjects or others at a **greater risk** of harm than was previously known or recognized, and are more likely than not, related to the research activity are to be used for this assessment. If these criteria are met the unanticipated problem should be reported to the IRB. Regardless of whether the adverse event is determined to be an unanticipated problem, the investigator must ensure that the adverse event is reported to the sponsor and FDA if applicable (e.g., the PI is the holder of the IND or IDE), promptly, within 10 working days of the date the investigator became aware of the event.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (e.g., due to an unexpectedly higher frequency of the event, the monitoring entity should report this determination to the investigator and the investigator should promptly report this to the IRB).

Other Site (External) AEs that meet the reportable criteria above, unexpected or unanticipated, serious, places subjects or others at a **greater risk** of harm than was previously known or recognized, ***(requires a significant change to the protocol, revising the Inclusion/Exclusion criteria, includes a new monitoring requirement, change in the informed consent or investigator brochure),*** and are more likely than not, related to the research activity. **These reports must be accompanied by**

(1) a clear description of why the AE or series of AE was determined to be an unanticipated event; and

(2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem. If all of these criteria are met the report should be forwarded to

the IRB within 10 working days of the date the investigator became aware of the event.

ALL Local fatalities, occurring with subjects on Active Treatment whether related or unrelated, must be reported to the IRB within 24 hours of the investigator becoming aware of the event. This 24 hour notification may be via phone, fax, email or report form and should be followed by a written report submitted through the eIRB system as soon as possible. Any (related) local fatality must be reported to the sponsor and the FDA, if applicable.

Unanticipated Problems- Investigators or the study team must report unanticipated problems to the RPO in writing using the appropriate Unanticipated Problem Report Forms found in the eIRB system.

The written report should contain the following:

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

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

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

As stated above an adverse event **not meeting the reportable criteria** may be reported to the IRB if the sponsor **requires** they be reported to the IRB. These reports may be submitted on the **"Sponsor Required but Otherwise Not Reportable Event Form (AE3)"** (See instructions for reporting unanticipated Problems/Adverse Events on the forms in the eIRB form library.

Sponsored Required (AE3) reports will be acknowledged as being received by the RPO office. The report form will be dated and acknowledged as received. An acknowledged copy of the report form only will be added to the PI research documents of the eIRB system. The sponsored required but otherwise not reportable form may be filled out and submitted. You can fill out one AE3 form

with the committee number; PI name and study title and then attach any reports you received from the sponsor that are not reportable, e.g. MedWatch forms, AE forms, a report or list of events. You should keep a list of what you attached, however, because you will only receive back an acknowledged report form, stamped and dated only, without attachments.

8.4.2 Review by IRB Staff and Chair

Upon receipt of a reportable Unanticipated Problem Report Form from a Principal Investigator, the RPO staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the RPO staff will contact the investigator or the designated contact person to obtain additional information.

Once this additional information is received from the investigator the RPO staff will forward all unanticipated problems that involved risk to participants or others as indicated on the report form to the chairperson and/or other experienced member(s) designated by the IRB chairperson. The IRB chairperson or designee reviews the report of the problem. The IRB chairperson (or designee) will make the final determination as to whether the problem is to be regarded as an unanticipated problem and involved risk to participants or others.

If the reviewer considers that either (1) the problem was foreseen OR (2) no participants or others were harmed AND participants or others are not at increased risk of harm, (e.g. the PI did not indicate changes were to be made to the protocol, ICD, IB, etc.), the reviewer signs the report form and does not check the box requesting further information or review by the full board. The reviewer acknowledges the report in the eIRB system and a letter of acknowledgement is forwarded to the investigator. The signed form is uploaded in the study filed electronically with the research documents in the eIRB system.

The IRB chairperson (or designee) has authority to require submission of more detailed contextual information from the PI, the sponsor, the study coordinating center, or DSMB/DMC about any unanticipated problem occurring in a research protocol as a condition of the continuation of the IRB's approval of the research. The IRB reviewer has access to all study documents in the eIRB system to make the determination of risk to participants or others.

After reviewing the materials, the reviewer will take appropriate action depending on the nature of the risk involved, including requesting the investigator modify the protocol or the consent form(s), if applicable. The results of the review will be recorded on the report form and filed in the eIRB study file.

If the unanticipated problem was deemed by the chair or designee to put subjects at risk based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB.

All reported unanticipated problems where subjects or others were placed at a greater risk than was previously known or recognized will be reviewed at a convened IRB meeting.

8.4.3 Convened IRB Review

If the unanticipated problem is reviewed at a convened IRB meeting the primary reviewers as well as the full board will have access in the eIRB system to all pertinent documents submitted by the PI regarding this event as well as all previously submitted study documents located in the eIRB study.

The full IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.
- **What action in response to the report is appropriate**
    a. Whether suspension or termination of approval is warranted.
    b. Whether notification to participants is warranted and if the information relates to their willingness to continue to participate in the study.
    c. Whether further reporting to Institutional and/or federal officials is required.

If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

- No action
- Requiring modifications to the protocol
- Revising the continuing review timetable
- Modifying the consent process
- Modifying the consent document
- Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
- Providing additional information to past participants
- Requiring additional training of the investigator and/or study staff
- Other actions appropriate for the local context

If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

- Requiring modifications to the protocol
- Revising the continuing review timetable
- Modifying the consent process
- Modifying the consent document

- Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)
- Providing additional information to past participants
- Requiring additional training of the investigator and/or study staff
- Reconsidering approval
- Requirement that current participants re-consent to participation
- Monitoring of the research
- Monitoring of the consent process
- Referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
- Suspending the research
- Suspending Enrollment in the Research until changes are made to the protocol, consent form or any other documents as applicable
- Terminating the research
- Other actions (corrective actions) appropriate for the local context

If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. See Section 3.10.1 of this Manual.

If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will vote that determination into the minutes and will:

a. Notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, and the Investigator's supervisor, and

b. Report its findings and recommendations to the relevant regulatory agencies and institutional officials according to the procedures in Section 11 of this Manual.

8.4.4 Reconsideration of the IRB Decision

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

If an investigator requests reconsideration, the investigator's written request is considered at the next IRB meeting and the IRB makes a determination whether to uphold, reverse or modify its decision. The IRB notifies the investigator of the final outcome.

If the IRB receives a request for reconsideration from the investigator, the IRB should notify the Senior Vice President and Chief Research Officer of the request and of the final outcome.

8.5 Data Safety Monitoring Plan

For all research the initial research plan submitted to the IRB should describe the procedures for safety monitoring, reporting of adverse events and/or unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the results to the IRB. This description should include information regarding an independent Data and Safety Monitoring Board (DSMB), if one exists, or an explanation why an independent data safety monitor is not necessary. See Section 3.15 of this Manual.

When the convened IRB reviews a Data Safety Management plan and requests modifications to the plan as presented the investigator must comply with the IRBs requests and present the revised plan to the convened IRB for review and approval.

9 Protocol Exceptions or Deviations

9.1 Policy

The Lifespan IRB's must be notified of any protocol deviations or exceptions that result in an increase in risk or a decrease in benefit to participants.

The following procedures describe how protocol exceptions and deviations are reported to the IRB.

9.2 Definitions

Exceptions - Protocol exceptions are defined as circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient/subject (example: patient/subject is allergic to one of the medications provided as supportive care). Usually it is a violation that is anticipated and happens with prior agreement from the sponsor.

Deviations - A protocol deviation is defined as a violation that is unanticipated and happens without any prior agreement (example: inclusion /exclusion criteria not followed, protocol visit scheduled outside protocol window, blood work drawn outside protocol window, etc.). The IRB will review these reports for frequency and may audit any protocol reporting frequent deviations.

9.3 Deviations

It is the responsibility of the Investigator not to deviate from the protocol approved by the IRB, except to avoid an immediate hazard to the participant. Changes to the protocol should be submitted as an amendment request to the IRB and receive written approval prior to implementation of the change.

Deviations that increase risk, have potential to recur, or are undertaken to eliminate an immediate hazard would be considered an Unanticipated Problem and should be handled according to Section 8.

Sponsors may require the PI to notify the sponsor and IRB of all unplanned deviations from IRB approved protocol procedures. The monitor of the sponsored study may determine certain deviations need not be reported to the IRB. It is the PI's responsibility to comply with the reporting requirements as determined by the sponsor.

For un-sponsored studies the investigator should submit all deviations from the protocol to the IRB or submit a DSMP/DMSB report indicating oversight determination the deviation(s) need not be reported to the IRB.

The GCP Guidance states that an investigator: should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects, or

when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)). [GCP 4.5.2. at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

When a sponsor requests that the IRB be notified of a deviation, the completed form should be submitted via the eIRB system. The deviation submission will be forwarded to the IRB chair or designate for review. Deviations from Protocol are issues of Non-Compliance. Major or repetitive deviations may be ruled by the IRB to constitute serious and/or continued non-compliance resulting in suspension of IRB approval.

9.4 Exceptions

The Investigator is responsible for reporting, exceptions made to the protocol to the IRB. The IRB will perform an expedited review of the "Protocol Deviation/Exception Report" form submitted by the Investigator along with documentation of Sponsor justification and approval.

These exceptions should be approved by the sponsor before being implemented. Notification to the IRB should occur as soon as possible.

Exceptions may not increase risk or decrease benefit, affect the participant's rights, safety, welfare, or affects the integrity of the resultant data.

9.5 Reporting & Review

Deviation/Exception Report forms are to be completed for those events that qualify as a protocol deviation or exception. These reports should be completed and submitted via the eIRB system. The IRB Chair/designate will review the documents and an acknowledgement will be sent back to the investigator. The Chair/designate may choose to place any deviation or exception on the agenda of the next convened IRB meeting for discussion. The investigator may be asked to appear at that meeting to answer any questions or clarify issues for the IRB.

10 Complaints and Non-compliance

10.1 Policy

Lifespan Institutional Review Boards are committed to protecting the rights and welfare of human subjects in research and sets forth the following procedure for the expeditious handling of concerns or complaints of non-compliance.

The following procedures describe how complaints, allegations of non-compliance, suspensions and terminations of IRB approval are handled by the IRB. In cases of serious non-compliance, including but not limited to cases that could rise to the level of Research Misconduct (as defined by federal law and by the Lifespan Policy on Research Misconduct), the IRB Chair, the RPO Director, or the Administrative Director of ORA will consult with the Office of the General Counsel and with the Lifespan Research Integrity Officer. Notwithstanding and with no intention to limit the IRB's charge to investigate and resolve all issues concerning the protection of human subjects in research, Lifespan reserves the right to handle some matters jointly with the IRB in cases where the problematic conduct rises to a level where additional institutional involvement is warranted.

10.2 Definitions

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

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

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

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

Finding of Non-Compliance - Finding of Non-Compliance is defined as an allegation of non-compliance that is proven true or a report of non-compliance that is clearly true. (For example, a finding on an audit of an unsigned consent document, or an admission of an investigator of that the protocol was willfully not

followed would represent reports of non-compliance that would require no further action to determine their truth and would therefore represent findings of non-compliance.)

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

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

10.3 Complaints

If the principal investigator (PI) or participant becomes aware of any complaints or concerns about a research protocol, they must notify the RPO promptly.

All complaints of non-compliance will be forwarded to the Chair of the Institutional Review Board (IRB).

The Chair of the IRB and the RPO Director will promptly handle (or delegate staff to handle), and, if necessary, investigate all complaints, concerns, and appeals received by the IRB concerning protection of human subjects in research. This includes complaints, concerns, and appeals from investigators, research participants and others. As referenced in Section 10.1, above, the Chair of the IRB, the Administrative Director of ORA or the RPO Director will provide notice to the Office of the General Counsel and the Research Integrity Officer when necessary, and will cooperate with Lifespan in coordinating any joint approach to handling the matter

Upon receipt of the complaint, the Chair will make a preliminary assessment whether the complaint warrants immediate suspension of the research project. If a suspension is warranted, the procedures in Section 3.10.1 will be followed.

If the complaint meets the definition of non-compliance, it will be considered an allegation of non-compliance according to section 10.4

If the complaint meets the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 8.

10.4 Non-compliance

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

The Principal Investigator is responsible for reporting any non-compliance by study personnel to the IRB. The maximum time allowed between the recognition of a reportable event and fulfilling reporting requirement is not more than 30 days.

10.4.1 Review of Allegations of Non-compliance

All allegations of non-compliance will be reviewed by the IRB Chair, the Director of the RPO, and the Administrative Director of the ORA. If an allegation of non-compliance is received, the Director will call a meeting with the IRB Chair. They will review all documents related to the allegation. These documents may include:

1. The last approval letter from the IRB
2. The last approved IRB application and protocol;
3. The last approved consent document
4. The grant, if applicable; and
5. Any other pertinent information (e.g., questionnaires, DSMB reports, etc.).

The IRB Chair and Director will review the allegation and make a determination as to the truthfulness of the allegation. They may request additional information or an audit of the research in question be conducted by the Research Compliance Program Manager.

If in the judgment of the IRB Chair and Director, the reported allegation of non-compliance is not true, no further action will be taken. If in the judgment of the IRB Chair and Director, the reported allegation of non-compliance is true, the non-compliance will be processed according to Section 10.4.2 Review of Findings of Non-compliance.

10.4.2 Review of Findings of Non-compliance

If in the judgment of the Director of the RPO and Chair the reported allegation of non-compliance is true, the Director will call a meeting with the Administrative Director of ORA and VP of Research.

If in the judgment of the IRB Chair and Director, any allegation or findings of non-compliance warrants suspension of the research before completion of any review or investigation to ensure protection of the rights and welfare of participants, the IRB Chair may suspend the research immediately as described in Section 3.10.1 with subsequent notification and review by the convened IRB and notification to the Administrative Director of the ORA and the VP of Research.

If in the judgment of the IRB Chair and Director, the reported finding indicate non-compliance and does not warrant immediate action to protect the rights and welfare of the research participants the IRB will be informed of the allegation and findings at the next convened meeting. All materials that were gathered as a part of the investigation will be provided to all members attending the IRB meeting. In

addition, all members will have access to the study documents in the eIRB system. All members will be expected to review these materials.

The convened IRB will confirm by vote on the findings to determine non-compliance. The IRB may find:

a. There is no issue of non-compliance
b. There is non-compliance that is neither serious nor continuing and an adequate corrective action plan is in place
c. There may be serious or continuing non-compliance and direct that a formal inquiry, described below, be held; or,
d. Request additional information.

If the IRB determines the issue requires immediate action they may vote to follow the steps in section 10.4.4 below. If the IRB determines more information is required they may follow the steps outlined below in section 10.4.3.

The process for management of serious or continuing non-compliance by the convened IRB, includes the maximum time allowed between the recognition of a reportable event and fulfilling the reporting requirement to the IRB by the PI is not more than 30 days.

10.4.3 Inquiry Procedures

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

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

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

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

In cases where Lifespan wishes to handle the matter jointly with the IRB, the charge of the subcommittee should be reviewed in advance with the Office of the General Counsel and with the Research Integrity Officer, if appropriate.

10.4.4 Final Review

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

1. Request a correction action plan from the investigator
2. Verification that participant selection is appropriate and observation of the actual informed consent process
3. An increase in data and safety monitoring of the research activity
4. Request a directed audit of targeted areas of concern
5. Request a status report after each participant receives intervention
6. Modify the continuing review cycle
7. Request additional Investigator and staff education
8. Notify current subjects, if the information about the non-compliance might affect their willingness to continue participation
9. Require modification of the protocol.
10. Require modification of the information disclosed during the consent process.
11. Require current participants to re-consent to participation.
12. Suspend the study
13. Terminate the study
14. Suspension or termination of IRB approval of other research protocols or of all research involving human subjects in which the investigator participates.
15. Recommend disciplinary action
16. Ban submission of future proposals by the investigator

The investigator is informed of the IRB determination and the basis for the determination in writing and is given a chance to respond. If the IRB determines that the non-compliance was serious or continuing, the results of the final review will be reported as described below in Section 11.

If warranted, the full committee will deliberate the findings and investigator response to determine if further investigation or reporting to other regulatory institutional or outside officials/committees is indicated.

The full committee, if warranted and in conjunction with other institutional officials, will make recommendations for appropriate disciplinary actions which may include but are not limited to the following: letter of rebuke, mandatory human subjects related education, time-limit suspension of protocol, permanent suspension of protocol, forward findings to the appropriate departments.

11 Reporting to Regulatory Agencies and Institutional Officials

11.1 Policy

Federal regulations require prompt reporting to appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval. The Lifespan HRPP will comply with this requirement and the following procedures describe how these reports are handled.

All reporting actions will occur within the minimal amount of time necessary to conduct a full investigation, however the report will be filed no more than 30 days from the time the HRPP determined that an event was reportable. In the case of an investigation not being completed within 30 days an initial report will be filed with a final report to follow when the investigation is completed.

11.2 Procedures

1. IRB staff will initiate these procedures as soon as the IRB takes any of the following actions:
   Determines that an event may be considered an unanticipated problem involving risks to participants or others
   Determines non-compliance was serious or continuing
   Suspends or terminates approval of research
2. The Director or designee is responsible for preparing reports or letters which includes the following information:
   a. The nature of the event (Unanticipated problem involving risks to participants or others, serious or continuing non-compliance, suspension or termination of approval of research)
   b. Name of the institution conducting the research
   c. Title of the research project and/or grant proposal in which the problem occurred
   d. Name of the principal investigator on the protocol
   e. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
   f. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
   g. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.)

h. Plans, if any, to send a follow-up or final report by a specific date or when an investigation has been completed or a corrective action plan has been implemented, whichever comes first

3. The IRB Chair and the Institutional Official may review the letter and modify the letter/report as needed.
4. The Institutional Official or designate is the signatory for all correspondence from the facility.
5. The Director or designee sends a copy of the report to:
   a. The study in the eIRB system
   b. The Institutional Official
   c. The following federal agencies:
   d. OHRP, if the study is subject to DHHS regulations or subject to a DHHS Federal Wide Assurance
   e. FDA, if the study is subject to FDA regulations. (Reporting to FDA is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.)
   f. If the study is conducted or funded by any Federal Agency other than DHHS that is subject to “The Common Rule”, the report is sent to OHRP or the head of the agency as required by the agency
   g. Principal investigator
   h. Sponsor, if the study is sponsored
   i. Department Head of the principal investigator
   j. Office of Risk Management, if appropriate
   k. Others as deemed appropriate by the Institutional Official

12 Investigator Responsibilities

12.1 Purpose

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

12.2 Investigators

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

12.2.1 Principal Investigators

At Lifespan, only Lifespan employees and all employed members of physician corporations with Administrative, Supervisory and Teaching Services Agreements (AS & T) which agree to research governance, conducting research on-site or off-site with the approval of various compliance committees, may serve as the Principal Investigator or as the sponsor on a research project involving human subjects. Exceptions to this eligibility criterion will be made through the use of a separate research governance agreement. A PI will typically have a level of expertise as evidenced through their achievement of an advanced degree.

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

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

12.2.2 Residents/Fellows/Student Investigators

Residents, Fellows or Students may not serve as Principal Investigators. They must have a Lifespan mentor who fulfills the PI eligibility criteria and who will serve as Principal Investigator and faculty advisor on the study. Residents and Fellows will be considered Principal Researcher(s).

12.2.3 Research Team

The research team is the PI and other individuals, also known as key personnel, who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the protocol. Key personnel are individuals who interact with research participants and/or their identifiable data.

12.3 Responsibilities

The Principle investigator is responsible to conduct research in accordance with all federal applicable regulations as defined in 45 CFR 46, 21 CFR 11, 50, 54, 56, 312, 812. Principle investigators are also responsible to comply with the State of Rhode Island Rules and Regulations for Licensing Hospitals (R23-17-HOSP), Section 16.0, “Research Involving Human Subjects”.

Research performed under the auspices of the Hospital involving human subjects, conducted by employees or members of an affiliated practice plan foundation, or other approved relationships, whether supported by outside funds or not, must be formally reviewed and approved by the IRB prior to commencement. Further guidance may be found under LS Corporate Compliance Policy CCPM – 23.

The investigator is also responsible for complying with all state regulations which include:

a. Ensuring that a written protocol for each research study which, at a minimum, describes the nature and purpose of the study, the procedures to be utilized, the extent and type of assessment/testing/procedures of the subjects, the risks and benefits, if any, of participation, the content of and subject’s access to records to be maintained and provisions regarding confidentiality, disclosure of the research information, and a data safety/monitoring plan.

b. Advising each subject of the items listed in Section 16.2(a), as well as his/her rights and responsibilities, and shall agree to participate in the research study. The use of written consent shall apply to all research participants, except those identified in the federal guides (45 CFR 46.116-46.117) where the requirement for written consent has been explicitly waived by the hospital’s IRB. Also, written consent shall not be required for studies that are exempt from IRB review (45 CFR 46.101). Studies conducted using information abstracted from existing records in anonymous form shall not have a requirement of directly contacting individuals involved in the research.

c. Hospital standards and procedures shall be observed in all clinical activities involving research subject (e.g. phlebotomy or other specimen collection, EKG, etc.) unless deviation from standard procedures is integral to the research, in which case this shall be described in the written study protocol and subsequently approved by the IRB.

d. The principle investigator will ensure that he/she works with the appropriate pharmacy representative to comply with procedures pertaining to the control, accountability, security, administration and maintenance of records of receipt and disposition of all drug and biologicals used in each study. Please refer to the Pharmacy (PH207) Services Policy, “Clinical Investigational Drug Trials”.

e. If the principle investigator and his/her staff become aware of any clinical condition/concern which may warrant further assessment or treatment, he/she will promptly notify the subject and advise follow-up with a health care provider.

   If appropriate, an Unanticipated Problem/Event Form will be submitted to the IRB and sponsor. At all times, the subject has the right to withdraw from the study.

f. Investigators are to maintain records regarding a subject in conformance with the written study protocol. Subject records, either original or accurate reproductions, shall be maintained for at least 5 years, or longer, if required by the sponsor. HIPAA requires maintaining identifiable records for 6 years.

g. All investigators and their staff are required to complete a training program in human subject protection. Additionally all investigators are to make sure that all staff participating in a research study have received training in the specific protocols to be applied. The Principle investigator will be asked to complete a check box on the initial application form for Committee Review, attesting to such training. Through the annual review process, the Principle investigator will also need to provide a statement regarding training in the specific protocol.

h. Each protocol will have a quality assurance program in effect to ensure conformance to the written study protocols. The research proposed should describe the investigators' plans for a data safety/monitoring board or any other quality assurance program as appropriate.

12.4 Good Clinical Practice Guidelines

When a principal investigator receives a Human Subject Protection Approval letter from the Lifespan IRB, they are notified that this institution requires the investigator to comply with the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines as they correspond to the FDA/DHHS regulations.

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

1. develop and conduct research that is in accordance with the ethical principles in the Belmont Report

   http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

2. develop a research plan that is scientifically sound and minimizes risk to the subjects;

a. clinical trials should be scientifically sound and described in a clear and detailed protocol ***GCP 2.5***

b. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society***.*** ***GCP 2.2***

c. A trial should be initiated and continued only if the anticipated benefits justify the risks. The IRB determines that the alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks have been disclosed to the participants. ***GCP 2.2, GCP 4.8.10(i).***

d. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial. ***GCP2.4***

e. Investigational product should be manufactured, handled, and stored in accordance with applicable good manufacturing practice.

3. have sufficient resources necessary to protect human subjects, including:

a. Access to a population that would allow recruitment of the required number of subjects. ***GCP 4.2.1***

b. Sufficient time to conduct and complete the research. ***GCP 4.2.2***

c. Adequate numbers of qualified staff (each individual involved in conducting a trial should be qualified by education, training and experience to perform their respective tasks) ***21 CFR 312.53(g); GCP 2.8, 4.2.3***

d. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial related duties GCP ***4.1.5***

e. Adequate facilities. ***GCP 4.2.3***

f. A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions. ***GCP 4.2.4***

g. Availability of medical or psychological resources that subjects might require as a consequence of the research.

h. The research permits monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority. ***GCP 4.1.4***

i. The researcher maintains the clinical trial documents as specific in Essential Documents for the Conduct of a Clinical Trial (Section 8 of GCP guidance) and as required by the applicable regulatory requirements. ***GCP 4.9.4***

4. Assure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise

qualified to perform such under the laws of Rhode Island and the policies of Lifespan and its affiliates. ***GCP 2.8***

a. A qualified physician, who is an investigator or a sub investigator, for the trial should be responsible for all trial-related medical decisions ***GCP 2.7, 4.3.1***

b. During and following a subject's participating in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness of which the investigator becomes aware ***GCP 4.3.2; R23-17-HOSP 16.2(e)***

c. Maintain an up to date curriculum vitae of all necessary co-investigators as evidence of qualifications ***GCP 4.1.1, 8.2.10, 8.3.5***

d. Where allowed or required, the investigator may assign some or all duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator. ***GCP 4.6.2***

e. The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants. ***GCP 4.6.3***

f. Investigators should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor. ***GCP 4.6.3***

5. Assure that all key personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based. NIH requirement

a. List all of the persons in direct contact with the subject, or their identifiable data, on the abstract submitted to the RPO so that IRB staff can check that all Human Subject Protection training have been successfully completed as required by federal regulation ***GCP 4.1.5***

b. HSP training is required of all key personnel before the study can be approved by the IRB, and re-certification is required every 3 years. See below, 12.5.2, for exceptions to the re-certification rule.

c. HIPAA for research is an annual requirement for all Lifespan research personnel

d. HIPAA security certification is required annually of all PI's

6. Protect the rights and welfare of prospective subjects;
    a. It is recommended that the investigator inform the subjects primary physician about participation in the trial if the subject agrees ***GCP 4.3.3***
    b. Makes reasonable efforts to ascertain why a subject withdraws from the trial while respecting the subject rights ***GCP 4.3.4***
    c. That the investigator should be thoroughly familiar with the appropriate use of any investigational product, as described in the protocol, in the current Investigator Brochure, in the product information and in any other source provided by a sponsor ***GCP 4.1.2***
7. Have plans to monitor the data collected for the safety of research subjects,
    a) Investigators are required to outline how this will be accomplished on the initial application as a DSMP and in some cases a DSMB will be required by the IRB ***GCP 1.25***
    b) Records identifying the subject will be kept confidential in a locked cabinet inside a locked room with secure access. ***GCP 2.10, 2.11; Lifespan CCPM-55***
    c) Any results published will not include the subjects name unless otherwise granted in writing by a subject
    d) That the investigator ensures the accuracy, completeness, legibility and timeliness of any reported data ***21 CFR 312.64(b)***, ***GCP 4.9.1, 8.1***
    e) That any corrections or changes to the data recorded should be dated, initialed and explained if necessary, and should never obscure the original entry. ***21 CFR 312.64(b); GCP 4.9.3***
    f) The investigator should maintain the trial documents as required by the applicable regulations/requirements. These vary according to the source. ***GCP 4.9.5*** The State of RI requires research records be maintained for a minimum of 5 years. ***R23-17-HOSP 16.2(f)*** The PI is responsible to be aware of and adhere to all of the record retention requirements for his/her particular study. ***21 CFR 312.62(c)***
    g) The investigator should take measures to prevent accidental or premature destruction of these documents ***GCP 4.9.4***
8. Have a procedure to receive complaints or requests for additional information from subjects and respond appropriately, ***45 CFR 46.116(7)***
    a. List the local contact person and contact number in the IC for both the investigator and the Director, Research Protection Office.
9. Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and research staff;

a. researchers should be familiar with all research regulations and additional resource information can be obtained by contacting the ORA at 444-5843

b. all investigators and research staff should review the following online links regarding FDA, OHRP, GCP and RI regulations:

http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

http://www.hhs.gov/ohrp/

http://www.fda.gov/Drugs/default.htm

10. Recruit subjects in a fair and equitable manner

a. subject recruitment based on scientific justification

b. have appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research

c. subject payments are fair and appropriate

d. all recruitment materials are submitted to the IRB for review

11. Obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent; this is an ongoing process***21 CFR 50.27(a), 21 CFR 312.60; 45 CFR 46.117(a); GCP 2.9, 4.8.1, 4.8.8***

a. Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the participant of by the participant's legally acceptable representative. Prior to a participant's' participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion. Only an unexpired IRB approved, stamped consent form may be used to obtain consent. GCP 4.8.8

b. The ICD should be maintained with the regulatory documents, a copy should be obtained to use to consent subjects

i. ***GCP 3.3.6, 4.4.1, 8.3.3, 8.3.4***

c. The top right hand corner of each page of the ICD should be initialed by the person signing the ICD

d. . Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document and any other written information provided to the participants. GCP 4.8.11

e. For subjects who are in-patients, out-patients, clinic or emergency department patients, on an active investigational drug/device, a signed copy of the ICD must be placed the electronic medical records ***21 CFR 312.62(b)***

f. Telephone consent is never acceptable for research unless the IRB has waived documentation of consent. A FAX consent is allowable under certain circumstances ***21 CFR 50.27***

g. Consent must be obtained PRIOR to the initiation of any portion of the research protocol ***GCP 2.9***

h. The most current template obtained from the eIRB website or e-library of forms, must be used each time the investigator develops a consent form

i. All consent forms for studies conducted at Lifespan, must use the Lifespan template unless given a variance by the IRB

j. All consent forms should be written in language understandable to the subject you are seeking to enroll, it should be at a 6-8th grade reading level and in the subjects' native language

k. If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written consent document and any other written information to be provided to participants or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document. The witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that consent was freely given by the participant of the participant's legally acceptable representative.

l. Consent forms must be obtained by the investigator or their designate. A designate is defined as a member of the research staff who is certified in the protection of human subjects and has sufficient knowledge of the research to answer all of the questions posed by the subject

m. When adults are unable to consent, the IRB determines:

    1. A non-therapeutic clinical trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written consent document.

    2. Non-therapeutic clinical trials may be conducted in participants with a legally acceptable representative provided the following conditions are fulfilled:

- The objectives of the clinical trial cannot be met by means of a trial in participants wo can give consent personally
- The foreseeable risks to the participants are low.
- The negative impact on the participant's wellbeing is minimized and low.
- The clinical trial is not prohibited by law.
- The opinion of the IRB is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.
- Such trial, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly y closely monitored and should be withdrawn if they appear to be unduly distressed. GCP4.8.14

n. The consent must inform the participant that the monitor, the auditor, the IRB, and the regulatory authority will be granted direct access to the participant's original medical records for verification of clinical trial procedures or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the participant or the participant's legally acceptable representative is authorizing such access. GCP 4.8.10(n)

12. Ensure that all research involving human subjects receives IRB review and approval in writing before commencement of the research;
    a. maintain a regulatory binder where all the documents required for the trial should be kept including: ***GCP 2.10, 4.9.4***
        i. Investigator Brochure ***GCP 7.1, 8.2.1, 8.2.3***
        ii. IRB approved protocol ***GCP 8.2.2***
        iii. Approved and stamped Informed Consents (make copies for enrolling subjects)
            1. ***GCP 8.2.7, 8.3.3***
        iv. Advertisements used for recruitment
        v. Financial agreements, contracts and/or agreements
        vi. CV's of investigators updated to within 2 years ***GCP 4.1.1, 8.2.10***
        vii. Certification of mandatory human subjects protection training for PI and staff

viii. Normal lab values and/or tests included in the protocol if applicable ***GCP 8.2.11, 8.3.***6

ix. Sample of label for device (if used) ***21 CFR 312.62(a)***

x. Instructions for handling of study product and/or trial related material ***GCP 4.6.1, 4.6.2, 4.6.3, 8.4.1***

xi. Shipping records of product used for trial if applicable ***21 CFR 312.62(a); GCP 8.2.15***

xii. Decoding procedure for blinded trials and master randomization list when applicable

xiii. Monitoring reports when applicable

b. Update any documents as the trial progresses, maintaining original of all approvals ***GCP 4.9.4***

c. maintain all essential documents which permit the evaluation of the conduct of the trial and the quality of the data produced

13. Comply with all IRB decisions, conditions, and requirements;

a. all correspondence pertaining to the trial should be maintained with study files ***GCP 4.9.4***

b. maintain all correspondence that verifies any notification by the sponsor and/or PI to the IRB for safety updates, interim reports, AE's, deviations, monitoring visit reports and any regulatory notifications

14. Ensure that protocols receive timely continuing IRB review and approval;

a. Adding the following documents to the Regulatory/Study files as they become available:

i. Updates to the Investigator Brochure (IB) ***GCP 8.3.2***

ii. Any revisions to the protocol, CRF's, ICD and ads etc. ***GCP 8.3.2***

iii. Signed ICD's ***GCP 4.8.8, 8.3.3***

iv. Updates to any lab/medical/technical certifications, accreditation or validations ***GCP 8.3.6***

v. Certification of any new staff regarding mandatory Human Subject Protection (HSP) training

vi. Annual HIPAA Security certification for PI

vii. Subject screening log

viii. Subject ID code list ***GCP 8.3.21, 8.4.3***

ix. Subject enrollment log ***GCP 8.3.20***

x. Staff signature log ***GCP 4.1.5, 8.3.4***

xi. Signed, dated and completed CRF's

15. Report unexpected or serious adverse events problems that require prompt reporting to the IRB ***21 CFR 312.32, 312.53 (vii), 312.64(b), 312.66; 21CFR812.150; GCP 1.50, 4.11.1***

    a. Investigators must promptly report (according to the schedule in Section 8) the following events to the IRB:

    b. Adverse events of unanticipated problems which in the opinion of the principal investigator are both unexpected and serious are related to the research activity and involved risk to participants.

    c. An unanticipated problem or event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk

    d. Information that indicates a change to the risks or potential benefits of the research. For example:

        i. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

        ii. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.

        iii. A breach of confidentiality. (e.g., loss of a laptop containing identifiable research information)

16. Obtain IRB review and approval in writing before changes are made to approved protocols or consent forms ***21 CFR 312.53(vii), GCP 4.5.2, 8.2.7***

    a) The investigator should conduct the trial in strict compliance with the protocol as approved by the IRB ***GCP 4.5.1***

    b) The PI should not implement any deviation from, or changes to, the protocol without first notifying the IRB and receiving approval except where necessary to eliminate an immediate hazard to the subject ***GCP 4.5.2***

    c) document and explain any deviation from the approved protocol by submitted a Deviation Report to the IRB ***GCP 4.5.2, 4.5.3***

17. Seek IRB assistance when in doubt about whether proposed research requires IRB review – contact Director, Research Protection Office at 444-6897

12.5 Training / Ongoing Education of Investigators and Research Team

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

12.5.1 Initial Education

The Lifespan affiliate IRBs have contracted with a group of collaborating professionals through the University of Miami to manage and provide the necessary educational materials for Investigators engaged in research involving humans. The **Collaborative Investigator Training Initiative** (CITI) is a required course for Investigators and key study personnel to fulfill Lifespan's research education requirements. Human research protections education must be completed prior to initiating and IRB approved protocol.

New research protocols and applications for continuing review will not be accepted from principal investigators who have not completed the initial education requirement. New Investigators who have taken a human subjects protection course within 3 years at another location must present certification of this training. Most other "initial" HSP courses will be accepted.

The PI, investigators and key personnel (all individuals that will interact with research participants or their identifiable information) must complete the Lifespan Required Core Modules in CITI Course in the Protection of Human Research Subjects. Included in these modules are links to "Lifespan Policy and Procedure Manual for Human Research Protection," the "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.

Certification of human subject's education must be submitted to the Lifespan RPO by providing the date of successful completion of the appropriate CITI course(s) before authorization to conduct research at Lifespan is granted. In addition, in accordance with Rhode Island State regulations 23-17-16.2(g), it is the responsibility of the principal investigator to insure that all research staff conducting research studies, receive training in the specific protocols.

While research protocols and applications for continuing review will be accepted and reviewed if the Principal Investigator holds a current certification of training, final approval will not be granted until all co-investigators and members of the research team have completed the initial education requirement.

Currently, the CITI program offers our researchers a basic human subject protection course, HIPAA education for researchers, as well as re-certification courses. A Good Clinical Practice (GCP) course, Responsible conduct of Research course and a DNA course are also available to our research community through this CITI program. As the CITI curriculum is expandable,

please check the Lifespan website for other courses that may be added from time to time.

Documentation of Initial Education

If investigators and key personnel of their research team can verify that they have successfully completed human subject's research training equivalent to that required by Lifespan, they must supply the Research Protection Office with certification. All investigators or members of their research team must complete the requirements of Continuing Education.

12.5.2 Continuing Education and Recertification

To ensure that researchers maintain their knowledge of human subject protection in research, the Research Protection Office (RPO) requires human subject protection re-certification every three years. Upon reaching the 3 year anniversary of human subject certification, CITI will notify researchers that they need to re-certify. All active researchers and key personnel must re-certify through the CITI refresher online program. Failure to comply with this mandatory re-certification may restrict your privileges to conduct human subject research. Continued non-compliance may require the IRB to forward a report to the appropriate regulatory agencies and study sponsors.

12.5.3 Additional Resources

Human research protection information will be made available on the eIRB system in the forms library as well as on ORA/RPO website on an ongoing basis to ensure that Lifespan research community is apprised of current regulatory and policy requirements and training opportunities.

Continuing educational opportunities for the research community include an ORA newsletter that is circulated periodically. This newsletter contains information concerning ethical review of research and the latest issues related to such reviews. In addition, relevant information concerning the research review is available from the ORA web page at www.Lifespan.org/research/ and the eIRB system. These web pages contain guidelines and instructions for the application and review process of both clinical and bench research, as well as links to other sites such as Center Watch, NIH, and PRIM&R.

12.5.4 Investigator Concerns

Investigators or other researchers who have concerns or suggestions regarding the Lifespan human research protection program should convey them to the IRB Chairperson, Director, RPO, the Administrative Director of ORA, or the Senior Vice President and Chief Research Officer. In addition, the Director, RPO will be available to address investigators' questions, concerns and suggestions. If the gravity of the issue is such that it warrants further review, the investigator will be invited to the IRB meeting for formal committee review.

13 Sponsored Research

13.1 Policy

It is Lifespan policy that any sponsored research conducted at Lifespan is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that all sponsored research meets this requirement.

13.2 Definitions

Sponsor - Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management, or financing of a research study.

Sponsored research - Sponsored research means research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices or biologics.

13.3 Responsibility

1) Sponsor contracts are reviewed by the Office of Research Administration, Clinical Trials Office (CTO) and/or Grants and Contracts (G&C) – further guidance for research administrators is found in Policy ORA G&C 003.
2) The CTO/G&C will review contracts; and the RPO and CTO/G&C will share contract and study information as necessary for each sponsored protocol to ensure that protocol, consent, and contract language is consistent.
3) To further protect human research subjects, contracts will be for the following:
    a) All sponsor contracts will indicate that Lifespan will follow the protocol, applicable regulations and its ethical standards.
    b) All sponsor contracts will define who will be responsible for research related injuries.
    c) Sponsors will be requested to report to Lifespan, generally within 30 days, any findings detected during the monitoring process that could affect the health and safety of participants or their willingness to continue to participate, influence the conduct of the study, or alter the IRB's approval to continue the study. If such information is communicated by the sponsor to the PI directly, the PI has the responsibility to promptly notify both the IRB office and the CTO/Grants & Contracts office of such information.
    d) In addition, when participant safety could be directly affected by study results during and for a period of at least two years after completion of the study, Sponsors are required, via the clinical trial agreement, to notify the Institution/Researcher (in a timely manner appropriate to the level of risk), who will then determine the best course of action with regard to her/his research subjects. Language in the Clinical Trial Agreement will specify the time frame for reporting.

14 Conflict of Interest in Research

14.1 Purpose

It is Lifespan's policy to preserve public trust in the integrity and quality of research at Lifespan by minimizing actual or perceived conflict of interest in the conduct of research.

The following describe the procedures by which this responsibility is carried out.

14.2 Definitions

A. ***Financial interest*** means anything of monetary value whether or not the value is readily ascertainable.

B. ***Significant financial interest*** (SFI) means:

1. A financial interest consisting of one or more of the following interests of the Investigator (and those of the Investigator's spouse and dependent children) that reasonably appears to be related to the investigator's institutional responsibilities:

    a. With regard to any publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value;

    b. With regard to any non-publicly traded entity, a SFI exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated, exceeds $5,000, or when the Investigator (or the Investigator's spouse or dependent children) holds **any** equity interest (e.g., stock, stock option, or other ownership interest); or

    c. Intellectual property rights and interests (e.g., patents, copyrights), **upon receipt of income** related to such rights and interests (**Note:** $5,000 *de minimis* exception does not apply).

2. If PHS funded, Investigators also must disclose the occurrence of any reimbursed or sponsored travel (i.e., that which is paid on behalf of the

Investigator and not reimbursed to the Investigator so that the exact monetary value may not be readily available), related to their institutional responsibilities. This disclosure requirement does not apply to travel that is reimbursed or sponsored by a Federal, state, or local government agency, an Institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an Institution of higher education.

3. The term SFI does not include the following types of financial interests:

- salary, royalties, or other remuneration paid by Lifespan or its affiliates to the Investigator if the Investigator is currently employed or otherwise appointed by the Lifespan entity, including intellectual property rights assigned to the Lifespan entity and agreements to share in royalties related to such rights;
- income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles;
- income from seminars, lectures, or teaching engagements sponsored by a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education; or
- income from service on advisory committees or review panels for a Federal, state, or local government agency, an institution of higher education as defined at 20 U.S.C. 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education.

C. Financial conflict of interest (FCOI) means a significant financial interest that could directly and significantly affect the design, conduct, or reporting of research.

Conflict of Interest. A conflict of interest (COI) occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings.

A financial conflict of interest exists when the Institution, guided by the Lifespan Research Conflict of Interest Committee (LRCOIC), reasonably determines that a Significant Financial Interest could directly and significantly affect the design, review, conduct, results or reporting of the research. Any conflict of interest must be resolved by the Institution before a grant can be activated and/or before the research project may commence.

In addition, the LRCOIC committee will consider instances of Non-Financial Conflict of Interest in their deliberations. A Non-Financial Conflict of Interest may exist when an individual serves dual roles, such as health care provider and investigator. Other interests such as publication, promotion, or tenure can also become conflicts of interest that may affect an individual's judgment. Membership in oversight committees such as the IRB, as well as positions of authority, may pose potential conflicts of interest. Any position that includes responsibilities for the review and approval of research projects or contracts, other than their own, may potentially affect the design, decisions made, and/or action taken surrounding a specific study.

14.3 Individual Conflicts of Interest

These procedures apply to both financial and non-financial conflicts of interest and are guided by Code of Federal Regulations (Title 42 of the Code of Federal Regulations (CFR) Part 50 Subpart F) that promotes objectivity in research to ensure conflict of interests do not adversely affect the protection of participants or the credibility of the Lifespan Human Research Protection Program (HRPP).

For clinical studies involving the use of new human drugs and biological products or medical devices, certifications and disclosure requirements are defined in Food and Drug Administration (FDA) regulations, Title 21 CFR Part 54.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively disclosed and managed when they cannot be eliminated.

14.3.1 Procedures

14.3.1.1 Disclosure of Investigator COI:

The IRB application asks protocol-specific questions regarding significant conflict of interest for the investigators, key personnel, and their immediate families. The Principal Investigator must determine those individuals who serve as "Investigators" for the purpose of the Lifespan COI policy. The investigator is directed to the COI Process policy on the Office of Research Administration website http://www.lifespan.org/research/policies/docs/grantcontractpolicies/orageneral003coipolicy.pdf to determine COI based on the definitions indicated in this policy.

14.3.1.2 Evaluation of COI:

At the initial review of the research protocol, the research coordinator will review the application for the COI disclosure response. If a YES response is noted the application instructs the investigator to complete the COI registration form and contact the Administrative Director of the Office of Research Administration, who will process the disclosure through the LRCOIC.

Some points the LRCOIC Committee will consider are:

- How is the research supported or financed?
- Reported relationships between the sponsor and investigator and his/her immediate family members,
- By whom the study is designed?
- Will the institution receive any compensation? And,
- Is the institution an appropriate site for the research?

14.3.1.3 Management of COI:

The LRCOIC will determine if the significant conflict of interest is a financial conflict of interest and if the COI can be managed, reduced or eliminated. Some or all of the following actions may be taken:

- Disclosure of the financial conflict of interest to subjects through the consent process and form.
- Modification of the research protocol or safety monitoring plan.
- Monitoring of research by independent reviewers.
- Disqualification of the conflicted party from participation in all or a portion of the research.
- Appointment of a non-conflicted Principal Investigator to the study.
- Divestiture of significant financial interests by the Investigator and/or his/her immediate family member.
- Severance of relationships that create actual or potential conflicts.
- Prohibition of the conduct of the research at Lifespan.

If the investigator involved in the financial COI proposes to use human subjects in research related to the disclosed conflict, a convened IRB shall review the COI management plan. The IRB will have the opportunity to suggest changes. If the IRB feels that human subjects will not be protected by the COI management plan, they may recommend disapproval of the plan. The convened IRB will vote on the decision to approve or disapprove the study. The IRB Chair will communicate such a decision to the LRCOIC.

14.4 Institutional Conflict Of Interest

The policy of Lifespan is to ensure that the welfare of human subjects and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. The LRCOIC, through Lifespan's policies, is responsible for evaluating potential institutional conflict of interest and will take actions as required to avoid, or to appropriately manage, apparent institutional COI with regard to research projects.

14.4.1 Identification of Institutional Conflict of Interest

The LRCOIC is informed of all potential and real conflict of interest situations involving Lifespan held intellectual property, through the regular reporting of the Administrative Director, Lifespan Office of Research Administration (ORA) and the General Counsel's Office.

Additionally, through a separate collection of corporate leadership and physician leadership COI disclosures, the Senior Vice President and Chief Research Officer, Internal audit and Compliance compiles the annual disclosure statements. These are reviewed by the Senior Vice President and Chief Research Officer, Internal Audit and Compliance and the Administrative Director, Lifespan ORA. All disclosures involving research faculty or business relationships with research sponsors or licensees are brought to the LRCOIC for further investigation and review. The results of the findings of the LRCOIC are communicated to the IRB and through the Senior Vice President and Chief Research Officer, Internal Audit and Compliance, to the Lifespan Board of Directors, Compliance Committee.

14.4.2 Management of Institutional Conflict of Interest

As part of its review of institutional COI, the LRCOIC will ask if any related research involves human subjects. If yes, any conflict management plan which is developed will be forwarded to the IRB.

14.4.2.1 Assumption of conflict of interest

If Lifespan retains a significant financial interest, or if an institutional official with direct responsibility for the HRPP holds a significant financial conflict of interest in particular intellectual property, then the LRCOIC must assess the potential conflict of interest and weigh the magnitude of any risk to human participants. When reviewing potential institutional conflict of interest, the LRCOIC will assume an inclination against the conduct of human subject's research at, or under the auspices of, the institution where a COI appear to exist. However, the assumption may be overturned by the Committee when the circumstances are compelling and the Committee has approved an effective conflict management plan.

14.4.2.2 Decision making

A key aspect in decision-making is to analyze when it would be appropriate and in the public interest to accept and manage a COI, rather than require that the COI be eliminated. In some cases, the benefits of conducting a proposed research activity at the institution will be potentially high, and the risks will be low. In other cases, the scientific advantages of conducting the research may be speculative, and the risks may be great. In these latter instances, the conflict should be avoided by disapproving the research application.

14.4.2.3 Evaluation of risk

Each case should be evaluated based upon the following:

1. The nature of the science;
2. The nature of the interest;
3. How closely the interest is related to the research;
4. The degree of risk that the research poses to human participants; and
5. The degree to which the interest may be affected by the research.

The LRCOIC will consider whether the institution is uniquely qualified, by virtue of its attributes (e.g., special facilities or equipment, unique patient population, etc.) and the experience and expertise of its investigators, to conduct the research and safeguard the welfare of the human subjects involved.

14.4.2.4 Potential actions

Potential actions to be considered to better protect subjects are any (or a combination) of the following:

1. Public disclosure of the financial interest;
2. Not conducting proposed research each at that institution, or halting it if it has commenced;
3. Reducing or otherwise modifying the financial (equity or royalty) stake involved;
4. Increasing the segregation between the decision-making regarding the financial and research activities;
5. Requiring an independent data and safety monitoring committee or similar monitoring body;
6. Modifying role(s) of particular research staff or changes in location for certain research activities, (e.g., a change of the person who seeks consent, or a change in investigator); or
7. Establishing a research monitoring process so that the research can be closely scrutinized to ensure that potential conflicts do not undermine the integrity of the work and of Lifespan.

Further guidance regarding Conflict of Interest may be found in Lifespan Corporate Compliance Policy CCPM-9 and Research Conflict of Interest Policy ORA GEN 003. Additional guidance regarding interactions with drug and device companies may be found in Corporate Compliance Policy CCPM-46.

15 Participant Outreach

15.1 Policy

Lifespan is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of research involving human participants at Lifespan.

The following procedures describe how Lifespan fulfils that responsibility.

15.2 Responsibility

It is the responsibility of the Director, Research Protection Office to implement the procedures outlined below.

15.3 Outreach Resources and Educational Materials

Lifespan's HRPP dedicates a section of the internet website to research participants entitled "Helping our Hospitals take the best Care of You/Research". http://www.lifespan.org/services/clintrials/research/ This website includes resources, such as a list of ongoing research studies; Lifespan designed brochures (Research and Human Subject Protection at Lifespan), Research Headlines, a Research Spotlight, FAQ's about Research and links to OHRP and FDA.

Lifespan provides several relevant links to the Office for Human Research Protections (OHRP) campaign to inform the general public about research participation: http://www.hhs.gov/ohrp/education/index.html

. Participants, prospective participants, and community members may access this information from the "Participant Outreach Corner" to increase public awareness and educate potential research participants.

15.4 Evaluation

Lifespan periodically evaluates its outreach tools and makes changes when appropriate.

The Director, Research Protection Office meets with Media Relations to assess:

1. The scope, the content and the adequacy of our outreach tools
2. Whether the research community is using the website resources
3. Whether additional resources are needed to improve participant outreach activities

The results of this evaluation will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.

16 Health Insurance Portability and Accountability Act (HIPAA)

16.1 Policy

It is the policy of Lifespan to comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Health Information Technology Economic and Clinical Health Act (HITECH) and their implementing regulations, as amended from time to tome (collectively the term HIPAA, as used in this Chapter, refers to both HIPAA and HITECH and their implementing regulations). Protected Health Information (PHI) obtained by Lifespan affiliates may not be used internally or disclosed to any person or organization outside the hospital for research purposes without prior approval of the IRB. Lifespan researchers must also abide by all Lifespan ORA and corporate policies regarding HIPAA privacy and security. Go to: http://intra.lifespan.org/compliance/privacy/policies.htm to review corporate HIPAA policies.

The following describe the procedures for conducting research at Lifespan in accordance with HIPAA.

16.2 Definitions

Access - Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Authorization - An authorization is a detailed document that gives covered entities permission to use protected health information for specified purposes, which are generally other than treatment, payment, or health care operations, or to disclose protected health information to a third party specified by the individual.

Covered entity - Covered entity is the term applied to institutions that must comply with HIPAA. These include:

- Health plans
- Health care clearinghouses
- Health care providers who conduct certain financial and administrative transactions electronically. These electronic transactions are those for which standards have been adopted by the Secretary under HIPAA, such as electronic billing and fund transfers.

Common Rule - The Common Rule is a Federal Policy for the Protection of Human Subjects and provides the primary source of regulation for human subjects research. The rule was first published in 1991 and has been codified in separate regulations by 15 Federal departments and agencies. The Health and Human Services Regulations are set forth at 45 CFR Part 46.

De-Identified Information - De-Identified Information is health information that has been stripped of all eighteen identifiers set forth in HIPAA (see Section 16.4.3 of this Chapter). In general, de-identified information is information that does not identify an

individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual.

Deletion - Deletion is the removal, erasing, or expunging information or data from a record.

Disclosure - Disclosure is the release, transfer, provision of access to, or divulging in any other manner information outside of the covered entity. Therefore, Disclosure is to parties external to Lifespan which can include parties that are considered part of the Lifespan Organized Health Care Arrangement (OCHA).

Health Information - Health Information is any information created or received by a health care provider or health plan that relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or payment for the provision of health care to an individual.

Identifiable Health Information - Identifiable Health Information is of health information that includes one or more of the direct identifiers set forth in HIPAA (*see* Section 16.4.3 of this Chapter), including but not limited to, demographic information collected from an individual.

Limited Data Set - A Limited Data Set is a partially de-identified subset of an individual's protected health information. Creation of a Limited Data Set requires removal of sixteen direct identifiers (as set forth in HIPAA), but allows for the inclusion of certain dates, locations, and other codes or characteristics not explicitly excluded. Limited Data Sets can only be used or disclosed for research purposes if the person or institution using or receiving the information signs a Data Use Agreement obligating them to protect the confidentiality of the information **Minimum Necessary.** Minimum Necessary refers to the principle that any access should be limited to the minimum amount of information needed to accomplish the intended purpose of the use or disclosure.

Privacy Board - Privacy Board is the term used to describe a board comprised of members of varying backgrounds and appropriate professional competencies, as necessary, to review individual's private rights. The Privacy Board serves as an alternative to an IRB for privacy issues only. It cannot replace the IRB for Common Rule purposes.

Protected Health Information - Protected Health Information is individually identifiable health information transmitted or maintained electronically or in any other form or medium, except for education records or employment records, as excluded by HIPAA.

Preparatory Research - Preparatory Research is the method applied to developing or designing a research study.

Waiver of Authorization - Waiver of Authorization is a means of requesting approval from an IRB or Privacy Board rather than asking each research subject for an authorization to access protected health information.

16.3 Statement of Policy

PHI obtained at a Lifespan affiliate may *not* be used internally or disclosed to any persons or organizations outside the hospital for research purposes without the prior approval of the affiliate's designated IRB. All persons requesting access to PHI for research purposes must submit the request to their IRB. The IRB will be responsible for ensuring that strict policies and procedures regarding the access, use, and disclosure of PHI for research purposes are followed. This means that no research may be conducted by any affiliate staff, medical staff, or any other persons on the premises without the prior approval of the IRB.

Stringent HIPAA requirements apply to the use and disclosure of PHI in connection with human subjects' research. In general, the IRB may *not* authorize the use or disclosure of PHI for research purposes unless specific exceptions, outlined below, are met.
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16.4 Permitted Use or Disclosure of PHI in Research

Investigators may create, use or disclose PHI for research purposes in one of the following ways provided all legal and administrative requirements are met:

- Obtaining authorization from the individual or his or her legally authorized representative,
- Applying for a waiver of authorization
- De-identification of data
- With the creation of a limited data set
- Reviews Preparatory to Research
- Research on PHI of a decedent.

Each of these options is described below.

16.4.1 Authorization

HIPAA uses the term "authorization" to describe the process through which a participant allows Investigators to access PHI. An Investigator may seek such authorization from the participant or his or her authorized representative to create, use or disclose PHI. Regulations require that a valid authorization contain the following elements:

1. A description of the PHI to be used or disclosed;
2. The names of the person(s) authorized to make the requested use or disclosure;
3. The names of the person(s) to whom the covered entity may make the requested use or disclosure;
4. A description of each purpose of the requested use or disclosure;
5. Authorization expiration date or event;
6. Signature of the individual and date;
7. A statement of the individual's right to revoke his or her authorization;
8. A statement indicating whether treatment, payment, enrollment, or eligibility of benefits providing authorization; and

9. A statement of the potential risk that the PHI may be re-disclosed by the recipient.

Research Authorization documents address HIPAA/confidentiality requirements. HIPAA requirements pertain to the use and disclosure of PHI from Lifespan affiliates to other entities; therefore, revisions to meet sponsor requirements are usually not permitted.

The Research Authorization form may contain optional components on which an individual's ability to receive research-related treatment is not conditioned, such as an authorization to use protected health information collected for the research study in a separate database or tissue repository. Such "compound" Research Authorization forms must clearly distinguish between the conditioned and unconditioned authorization components and provide the individual an opportunity to "opt in" to the research activities described in the "unconditioned" authorization component.

The Research Authorization form may also provide for authorization for use or disclose of protected health information in future, undetermined research so long as the Research Authorization form provides sufficient information that it is reasonable for the individual to expect that his or her protected health information could be used or disclosed for such future research.

16.4.2 Waiver of Authorization for Use or Disclosure of Protected Health Information in Research

Under certain conditions, the IRB may approve access to use or disclosure PHI without obtaining authorization from the participant. The following conditions must be met before the IRB may grant the waiver of authorization:

- The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
- An adequate plan to protect health information identifiers from improper use and disclosure;
- An adequate plan to destroy identifiers at the earliest opportunity consistent with the conduct of the research; and
- Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the HIPAA.
- The research could not practicably be conducted without the waiver of or alteration; and
- The research could not practicably be conducted without access to and use of the PHI.

16.4.3 De-Identified Data

Under HIPAA information is considered to be "de-identified" if 18 specific identifiers set forth by HIPAA have been removed and there is no reasonable basis to believe that the

remaining information could be used to identify a person. Once patient information has been de-identified in accordance with HIPAA standards, it can be used and disclosed without the need to comply with other HIPAA requirements.

The 18 identifiers that must be removed for PHI to be considered de-identified are as follows:

1. names;
2. geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of a ZIP code;
3. all elements of dates (except year) for dates directly related to an individual (e.g., date of birth, admission);
4. telephone numbers;
5. fax numbers;
6. electronic mail addresses;
7. social security numbers;
8. medical record numbers;
9. health plan beneficiary numbers;
10. account numbers;
11. certificate/license numbers;
12. vehicle identifiers and serial numbers, including license plate numbers;
13. device identifiers and serial numbers;
14. web universal locators (URL's);
15. internet protocol (IP) address numbers;
16. biometric identifiers, including finger and voiceprints;
17. full-face photographic image and any comparable images; and
18. any other unique identifying number, characteristic, or code.

Additionally, in order for an Investigator to create a de-identified data set, he or she must agree to the same conditions as those involved in "preparatory to research" described below.

An Investigator may also choose to use the "statistical method" as a mechanism for creating a de-identified data set. The IRB may determine that health information is de-identified if an independent, qualified statistician:

- Determines that the risk of re-identification of the data, alone or in combination with other data, is very small; and
- Documents the methods and results by which the health information is de-identified, and the expert makes his/her determination of risk.

Note: the expert statistician may not be the researcher or anyone directly involved in the research study.

16.4.4 Limited Data Set

As an alternative to using fully de-identified information, HIPAA makes provisions for the creation of a limited data set which requires the removal of 16 direct identifiers but allows for the inclusion of dates, geographic location (not as specific as street address) and any other code or characteristic not explicitly excluded. Limited data sets require a Data Use Agreement between the institution and the Investigator and are most often utilized for retrospective chart reviews.

The Data Use Agreement establishes who is permitted to use or receive the limited data set and requires that the recipient agree to the following:

- Not to use or further disclose the information other than as permitted by the data use agreement or as otherwise required by law;
- Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the data use agreement;
- Report to the covered entity any use or disclosure of the information not provided for by its data use agreement of which it becomes aware;
- Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the limited data set recipient with respect to such information; and
- Not to identify the information or contact the individuals.

16.4.5 Review Preparatory to Research

Investigators interested in reviewing Lifespan PHI for research purposes must submit a Preparatory to Research document to the Research Protection Office to obtain permission prior to beginning their review. The following purposes for a Preparatory to research are applicable:

Investigators may access PHI for the purpose of preparing a research protocol (e.g., querying of databases for any type of PHI to determine if research is feasible) before IRB submission or approval; or, investigators may access PHI after IRB approval to query medical records or databases for screening purposes or chart reviews. In both cases the following conditions must apply:

- The use or disclosure of the PHI is sought solely for the purpose of preparing the research protocol;
- The PHI will not be removed from Lifespan; and
- The PHI is necessary for the purpose of the research study.

16.4.6 Research on the Protected Health Information of a Decedent

The IRB may permit the use and disclosure of the protected health information of a decedent for research purposes. In order to permit such a use or disclosure, the IRB must obtain representations from the Principal Investigator that the use or disclosure is sought *solely* for research on the protected health information of a decedent *(e.g.,* researchers may not request a decedent's medical history to obtain health information about a decedent's living relative) *and* that the

information for which use or disclosure is sought is necessary for the research purposes. Moreover, the Principal Investigator must provide, at the IRB's request, documentation of the death of any individuals about whom information is sought. Once 50 years have passed since an individual's death, individually identifiable health information about the individual is no longer considered protected health information, and it thus may be released without meeting the foregoing requirements.

16.5"Minimum Necessary" Standard

HIPAA has established that the use and disclosure of PHI in situations other than treatment, payment or healthcare operations must be kept to the minimum necessary to meet the need of the research project. In keeping with this approach, PHI collected during research under a "Waiver of Authorization" can only be used or disclosed to the extent that it is the minimum necessary. Research activities completed under a proper authorization is not subject to the minimum necessary standard for use and disclosure of PHI. It is, however, held to only that information agreed upon in the authorization.

16.6 Accounting of Disclosure Requirements

HIPAA grants rights to patients/research subjects to an accounting of disclosures of their medical information. Lifespan must provide a patient or research participant, upon request, with an accounting of all non-routine disclosures of PHI maintained in his/her medical or billing record made during the six years preceding the patient's request.

In the research context, the accounting rules apply whenever a disclosure of PHI is allowed to occur without or before a subject's authorization (such as when the IRB approves a Waiver of Authorization, Prep to Research or Decedent Data Review) Since the accounting is required by law, all researchers must comply and track all disclosures (including release, divulgence, transfer, or provision of access) of PHI to anyone outside the Lifespan Covered Entity.

The requirement to account for disclosures in the research context leads to a higher burden for researchers who are OCHA members as compared to those who are workforce members. This occurs because the access to PHI by workforce members is considered a "use" because they are part of Lifespan, whereas the access by the OCHA member in the research context is considered a "disclosure". No accounting is required for permitted uses of PHI at the present time.

See eIRB system (forms library) for accounting of disclosures information and instructions. Investigators should contact the Compliance and Training Specialist directly with questions regarding the tracking procedures for Lifespan.

- For Prep to Research and Decedent Data Review this applies if a sponsor or some other non-workforce person(s) helps with or performs the Prep to research.

- For Waiver of Authorization and Decedent Data Review this applies if PHI in any other format other than a limited data set or de-identified information is released, accessed by, transferred to, divulged or shown to someone other than a member of the Lifespan workforce. If de-identified information is released, accessed by, transferred to, divulged or shown to someone other than a member of the Lifespan workforce then no accounting is necessary.

16.7 Prohibition on Sale of Protected Health Information

An individual's protected health information may not be sold without such individual's authorization. This prohibition on sale of protected health information does not apply in cases in which the protected health information is disclosed for research purposes (under one of the applicable exceptions that allows such disclosure) **and** the only remuneration received by the covered entity disclosing the information is a reasonable cost-based fee to cover the cost to prepare and transmit the protected health information for such purposes. "Costs" include both direct and indirect costs, including labor, materials, and supplies for generating, storing, retrieving, and transmitting the protected health information, labor and supplies to ensure the protected health information is disclosed in a permissible manner, and related capital and overhead costs. Payments to a covered entity pursuant to research grants and contracts that require reporting of protected health information to the research sponsor or funding agency are not considered a "sale" of protected health information, so long as the covered entity's role under the contract or grant is not limited to collecting and transmitting such data to a researcher.

17 Special Topics

17.1 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are issued by the federal government to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. CoCs may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

The certificate goes beyond the consent form in ensuring confidentiality and anonymity. Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (usually as part of a criminal investigation of the subjects).

Any research project that collects personally identifiable, sensitive information and that has been approved by an IRB is eligible for a Certificate. Federal funding is not a prerequisite for a Certificate.

17.1.1 Statutory Basis for Protection

Protection against compelled disclosure of identifying information about subjects of biomedical, behavioral, clinical, and other research is provided by the Public Health Service Act §301(d), 42 U.S.C. §241(d):

"The Secretary may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, including research on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

17.1.2 Usage

Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to subjects.

Any investigator engaged in research in which sensitive information is gathered from human subjects (or any person who intends to engage in such research) may apply for a Certificate of Confidentiality. Research can be considered "sensitive" if it involves the collection of:

1. information about sexual attitudes, preferences, practices;
2. information about personal use of alcohol, drugs, or other addictive products;
3. information about illegal conduct;
4. information that could damage an individual's financial standing, employability, or reputation within the community;
5. information in a subject's medical record that could lead to social stigmatization or discrimination; or
6. information about a subject's psychological well-being or mental health.

This list is not exhaustive. In the informed consent form, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above. Every research project that includes human research subjects should explain how identifiable information will be used or disclosed, regardless of whether or not a Certificate is in effect.

17.1.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A Certificate protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures.

For example, a Certificate does not prevent researchers from voluntarily disclosing to appropriate authorities such matters as child abuse, a subject's threatened violence to self or others, or from reporting a communicable disease. However, if researchers intend to make such disclosures, this should be clearly stated in the informed consent form which research subjects are asked to sign.

In addition, a Certificate of Confidentiality does **not** authorize the person to whom it is issued to refuse to reveal the name or other identifying characteristics of a research subject if

- the subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;
- authorized personnel of the Department of Health and Human Services (DHHS) or FDA request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
- release of such information is required by the Federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

17.1.4 Application Procedures

Any person engaged in research collecting sensitive information from human research subjects may apply for a Certificate of Confidentiality. For most research, Certificates are obtained from NIH. If NIH funds the research project, the investigator may apply through the funding Institute. However, even if the research is not supported with NIH funding, the investigator may apply for a Certificate through the NIH Institute or Center (IC) funding research in a scientific area similar to the project.

1. If the research is conducting a sensitive research project that is covered by the AHRQ confidentiality statute (42 U.S.C. section299a-1(c) entitled “limitation on use of certain information”) or the Department of Justice confidentiality statute (42USC section 3789g), then a CoC is not required.
2. If there is an Investigational New Drug Application (IND) or an Investigational Drug Exemption (IDE), the sponsor can request a CoC from the FDA.

For more information, see the NIH Certificates of Confidentiality Kiosk (http://grants.nih.gov/grants/policy/coc/index.htm).

17.2 Mandatory Reporting

Certain Rhode Island laws require licensed physicians or, in some cases, employees of licensed health care facilities such as hospitals, to make “mandatory reports” to the state government if certain conditions or situations are observed among patients or research subjects. Some examples of situations or conditions that would require a mandatory report are evidence of: child abuse, elder abuse, occupationally acquired

disease, certain infectious or sexually transmitted diseases, or a gunshot wound. The nature of the mandatory report dictates to which branch of the state government it must be reported. For instance, suspected child abuse must be reported to the Department of Children, Youth and Families (DCYF), while suspected elder abuse would be reported to the Department of Elderly Affairs. For the most part, information on diseases would be reported to the Department of Health.

Questions about mandatory reporting should be referred either to the Lifespan Risk Management Department or to the Lifespan Office of the General Counsel.

In research situations where investigators believe they are reasonably likely to encounter information that would require a mandatory report, the mandatory reporting obligation and the processes that go along with it should be described clearly in the informed consent form and should be frankly discussed during the informed consent process. If such research projects involve minors and an assent form is used, the mandatory reporting obligation should also be described in the assent form and the matter should be discussed with the minor.

17.3 Genetic Studies

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

In studies involving genetic testing, several questions need to be addressed, including:

1. Will test results be given?
2. Will disease risk be quantified, including the limits on certainty of the testing?
3. Will a change in a family relationship be disclosed, such as mistaken paternity?
4. Does the subject or family member have the option not to know the results? How will this decision be recorded?
5. Could other clinically relevant information be uncovered by the study? How will disclosure of this added information occur?
6. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw DNA?
7. Is the subject permitted to participate in the study while refusing to have genetic testing (such as in a treatment study with a genetic testing component)?

For DNA banking studies, several questions need to be addressed, including:

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

17.4 Research Involving Coded Private Information or Biological Specimens

Lifespan policy is based on the OHRP guidance document entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" http://www.hhs.gov/ohrp/policy/biodata/index.html this document:

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

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

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

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

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

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

and

2. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    - the key to decipher the code is destroyed before the research begins;
    - the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS

regulations do not require the IRB to review and approve this agreement); data use agreement

- there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
- there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

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

17.5 Case Reports Requiring IRB Review

In general, an anecdotal report on a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and would not require IRB approval. Going beyond one's own practice to seek out and report cases seen by other clinicians creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore would be considered research and would require IRB approval.

17.5.1 Definitions

Single Case Report: The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition of a single patient. Case reports normally contain detailed information about an individual patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

Case Series: The external reporting (e.g., publication or poster/verbal presentation) of an interesting clinical situation or medical condition in a series of patients (i.e., more than one patient). Case series usually contain detailed information about each patient and may include demographic information and information on diagnosis, treatment, response to treatment, follow-up after treatment, as well as a discussion of existing relevant literature. The information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.

17.5.2 IRB Review

There currently exists no government guidance on whether case reports fall within the definition of research. It is Lifespan policy that a single case report does not fall within the Common Rule definition of research. However, a report on a series of cases may constitute research and may require IRB review and approval as well as informed consent and privacy authorization from the subjects/patients discussed in the case series.

Case Series not requiring IRB approval involves only individuals who are or who have been under the care of the proposed author and therefore do not meet the research definition.

Case Series requiring prior IRB approval involves individuals who are not currently or have not been under the care of the proposed author for the condition under discussion and therefore meet the definition of research and requires IRB approval as well as informed consent and authorization, unless these requirements are waived by the IRB.

The retrospective review or prospective collection of specific information on a series of patients in order to answer a research question does not meet the definition of a case series and would require prior IRB review and approval. Going beyond one's own clinical practice to seek out and report cases seen by other clinicians (even combining cases with colleagues within one's department) creates the appearance of a systematic investigation with the intent to contribute to generalizable knowledge and therefore would also be considered research and would require prior IRB review and approval.

17.6 International Research

The IRB will review all international research utilizing human participants to assure adequate provisions are in place to protect the rights and welfare of the participants.

Approval of research is permitted if "the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in 45 CFR 46."

The Lifespan affiliated IRB must receive and review the foreign institution or site's IRB review and approval of each study prior to the commencement of the research at the foreign institution or site.

For Federally funded research, approval of research for foreign institutions or sites "engaged" in research is only permitted if the foreign institution or site holds an Assurance with OHRP and local IRB review and approval is obtained.

Approval of research for foreign institutions or sites "not engaged" in research is only permitted if one or more of the following circumstances exist:

- When the foreign institution or site has an established IRB/IEC, the Investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB/IEC or provide documentation that the site's IRB/IEC has determined that approval is not necessary for the Investigator to conduct the proposed research at the site.

- When the foreign institution or site does not have an established IRB/IEC, a letter of cooperation must be obtained demonstrating that the appropriate institutional or oversight officials are permitting the research to be conducted at the performance site.
- IRB approval to conduct research at the foreign institution or site is contingent upon receiving documentation of the performance site's IRB/IEC determination, or letter of cooperation, as applicable.
- It is the responsibility of the Lifespan Investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
- It is the responsibility of the Lifespan Investigator and the foreign institution or site to notify the IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research participants, etc.).
- The IRB will consider local research context when reviewing international studies to assure protections are in place that are appropriate to the setting in which the research will be conducted.
- In the case where there is no local IRB review the IRB may require an expert consultant, either from the local country where the research is conducted or from an international organization, with the expertise or knowledge required to adequately evaluate the research in light of local context.
- The informed consent documents must be in a language understandable to the proposed participants. Therefore, the IRB will review the document and a back translation of the exact content contained in the foreign language informed consent document which must be provided by the Investigator, with the credentials of the translator detailed in the IRB application or amendment form. Verification of the back translation should be made available for the IRB file.

- Researchers should ensure that participants outside the US have the equivalent protections that participants would be afforded in the US. OHRP provides a compilation of regulations and guidelines that govern human subjects research in other countries, as well as standards from a number of international and regional organizations. For further information, see:

OHRP International Compilation of Human Subject Protections

- Researcher Responsibilities
  - When studies are conducted in other countries (i.e. outside the USA) researchers should be knowledgeable about the local laws and customs which apply to the research, and the cultural context in which they will be working. They should ensure that participants in international research are afforded equivalent protections to those participating in the US, and must describe their qualifications and preparation for the research that enable them to estimate and minimize risks to subjects.
- IRB Responsibilities

- Lifespan IRB review of international research adheres to the same policies applied to domestic (US) research, when appropriate. Additional legal or cultural expertise may be consulted by the IRB during its review, and the IRB will make those determinations required by the laws of the countries in which the research is conducted.

- For DoD sponsored research involving participants who are not U.S. citizens or DoD personnel, researchers must obtain and provide:
  - Permission of the host country.
  - Ethics review and approval by the host country
  - The laws, customs, and practices of the host country must be followed. DoD Directive 3216.2, para.4.9

17.6.1 Monitoring of Approved International Research:

The IRB is responsible for the ongoing review of international research conducted under its jurisdiction through the continuing review process in accordance with all applicable federal regulations.

The IRB will require documentation of regular correspondence between the Lifespan Investigator and the foreign institution or site and may require verification from sources other than the Lifespan Investigator that there have been no substantial changes in the research since its last review.

18 Additional Requirements for DoD-Supported Research

18.1 Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research

Human-subjects research that is supported by the Department of Defense (DoD) or one of its components (e.g., Departments of the Army, Air Force, and Navy and Marine Corps) through a contract, grant, cooperative agreement, or other arrangement with a Lifespan affiliate must comply with DoD Regulations for “Protection of Human Subjects” at 32 CFR 219 and with DoD Directive 3216.2 (November 8, 2011).

Research involving human subjects covered under this appendix shall also comply with applicable Federal and State laws and regulations. The information in this appendix will explain the additional requirements required when conducting DoD supported research including special protections for research participants as well as additional review and reporting requirements for both the investigator and the IRB. It is the responsibility of the Principal Investigator (PI) to ensure that all additional DoD requirements for human subject protection are met. At time of new submission to the IRB the researcher must complete Application Appendix # 3 which can be found in the forms and template section of the eIRB system.

Research is considered to involve the DoD when:

- The research is funded by a DoD Component, including cases where Lifespan is the recipient of a sub award from the direct recipient of DoD funds, or
- The research involves cooperation, collaboration, or other type of agreement with a DoD Component, or
- The research uses property, facilities, or assets of a DoD Component.
- The research participants will intentionally include personnel (military and or civilian) from a component of DoD.

Important Note: DoD policies and requirements do not apply when DoD personnel incidentally participate as subjects in research that is not supported by DoD, and DoD personnel are not an intended population of the research.

18.2 DoD Definitions

DoD-supported research involving human subjects- Research involving human subjects for which the Department of Defense is providing at least some of the resources. Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution.

Human subject- A living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information.

Research involving human subjects- Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information.

Research involving a human being as an experimental subject - An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects.

Research monitor - Individuals with expertise consonant with the nature of risk(s) identified within the research protocol, whose role is to protect the safety and well-being of human subjects. This can be a physician, or other healthcare provider designated to oversee a specific protocol that has been determined to be greater than minimal risk.

Minimal risk -Means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The phrase "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

18.3 DoD Directive 3216.2 Requirements

18.3.1 Education and Training-

DoD requires that all individuals involved in the “design, conduct, review, management of or approval of human subjects research” complete training in human subjects research. The Lifespan policy for human subjects’ research training (renewed every 3 years) meets the training requirements for many of the DoD Components. The PI should check with the specific DoD component for any specific requirements.

18.3.2 Scientific Review

Human subject research involving DoD Components requires documentation of scientific review prior to IRB review of new applications and substantive amendments. Scientific review should assess that research procedures are consistent with sound research design and likely to yield the expected results. The scientific review may be the review provided by the funding agency (including the DoD) or by an established internal review mechanism.

18.3.3 Research Monitor

The IRB is responsible for making the determination that the research is minimal risk or greater than minimal risk. For DoD-sponsored research involving greater than minimal risk to subjects, the DoD requires appointment of an independent research monitor. The research monitor has the authority to: a) Stop a research study in progress; b) Remove individuals from the study; c) Take any steps to protect the safety and well–being of subjects until the IRB can assess the research monitor’s report. The PI identifies a candidate for the position of research monitor, taking into account the nature and disciplinary focus of the study and the likely type of expertise required. The IRB reviews the information regarding the monitor and determines whether the individual meets the DoD requirements for educational and professional expertise. The IRB also ensures that the research monitor is independent of the research team.

18.3.4 International Research

In review of the research conducted outside of the United States the Lifespan IRB policy (see IRB policy 17.6 International Research) for international research meets the requirements of the DoD. Researchers should be knowledgeable about the local laws and customs which apply to the research and the cultural context in which they will be working. The researcher must obtain and provide permission of the host country and ethics review approval of the host country to the IRB.

18.3.5 Multi-site or Collaborative Research Requirements

Collaborating institutions in multi-site research must hold a federal wide assurance. The PI in conjunction with the IRB should ensure that a formal research agreement between the collaborating institutions includes a scope of work that specifies the roles and duties of each party. When developing a proposal for DoD funding or other support that involves other collaborating institutions, the PI should consult the sponsoring DoD Component and the IRB early in the process to identify additional requirements for multi-site research.

18.3.6 Provisions for Research Related Injury

The informed consent document must provide information regarding payment of medical expenses, provision of medical care, or compensation for research related injuries, consistent with the requirement of the Common Rule. The PI is responsible for informing the IRB if there are any requirements of the DoD Components for the provision of care in the case of research related injury. If the DoD language is stricter than the Common Rule or Lifespan policies this language would need to be reviewed by Lifespan General Counsel and would also need to be in alignment with the study agreement.

18.3.7 Limitations on Waiver of Consent and Exception from Informed Consent in Emergency Medicine

The requirement to obtain consent cannot be waived for any research using DoD funds and meeting the definition of research involving a human being as an experimental subject. This places limitations on research involving deception, decisionally impaired individuals, or research being conducted under emergency conditions where the subject is unable to provide consent. The Secretary of Defense may waive this consent requirement under specific circumstance.

Informed consent may be provided by a legally authorized representative (LAR) only if A) the subject lacks decision making capacity due to age, condition, or other reason to make a decision regarding consent to participant in the research; **AND** B) the IRB has determined that the research is intended to be beneficial to the individual participants.

18.3.8 Research Involving US Military as Military Personnel as Research Subjects

If the research will include US Military personnel as participants the PI must submit a research plan that incorporates additional safeguards to minimize undue influence from individuals within a potential participant's chain of command. The PI should consult the sponsoring DoD Component as needed, to assist in making provisions for these additional safeguards. DoD policies do not apply when US military personnel incidentally participate as subjects in a study that is not DoD-sponsored.

Research involving surveys or interviews with DoD personnel (military or civilian) or their families may require an additional level of DoD review. Surveys may require DoD Survey review and approval. The PI would be required to provide documentation of this review to the IRB for the DoD Component.

When research involves U.S. military personnel:

1. Officers are not permitted to influence the decision of their subordinates.
2. Officers and senior non-commissioned officers may not be present at the time of recruitment.
3. Officers and senior non-commissioned officers have a separate opportunity to participate.
4. When recruitment involves a percentage of a unit, an independent ombudsman is present.

When research involves U.S. military personnel, limitations on dual compensation:

1. Prohibit an individual from receiving pay of compensation for research during duty hours.
2. U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.
3. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
4. Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

18.3.9 Vulnerable Populations

DoD requires that the protection of Common Rule subpart B (pregnant women/fetuses), C (Prisoners), and D (children) be applied to all research it supports.

In addition the following are additional DoD considerations for these populations.

For purposes of applying Subpart B, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge." The applicability of Subpart B is limited to research involving pregnant women as participants in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as participants. Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

Research involving children cannot be exempt.

When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum. Research involving prisoners cannot be reviewed by the expedited procedure.

In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.

- The research presents no more than minimal risk.
- The research presents no more than an inconvenience to the participant.

If a participant becomes a prisoner and the investigator asserts to the IRB that it is in the best interest of the prisoner-participant to continue in the research while a prisoner, the IRB chair may determine that the prisoner-participant may continue to participate until the convened RB can review this request to approve a change in the research protocol and until the organizational office and the DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol.

• The convened IRB, upon receipt of notification that a previously enrolled human participant has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-participant can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-participant's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human participants from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-participant to continue to participate in the research. This approval is limited to the individual prisoner-participant and does not allow recruitment of prisoners as participants.

Research involving a detainee as a human participant is prohibited.

- This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.
- The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

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18.4 Other DoD specific requirements

Reporting requirements

Records maintained that document compliance or non-compliance with DoD requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component.

The following must be promptly reported to the Human Research Protections Office (HRPO) for the sponsoring component (within 30 days of the event)

- Determinations of serious or continuing noncompliance;
- Unanticipated problems involving risks to subjects or others;
- Study suspensions or terminations;
- Audits, inspections or investigations of DoD research;
- Results of the IRB continuing review;
- Changes to the reviewing IRB;
- Substantive amendments to the protocol. Amendment must be reviewed and approved by the HRPO of the DoD component prior to implementing the change to the study.

18.4 DoD Regulations and Guidance

32 CFR 219, Protection of Human Subjects
DoD Instruction 3216.02, Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research, November 8, 2011
10 USC 980, Limitations on the Use of Humans as Experimental Subjects
Department of Defense Directive 3210.7, Research Integrity and Misconduct
Department of Defense Directive 6200.2, Use of Investigational New Drugs in Force Health Protection

The DoD regulatory and guidance resources cited here are key resources regarding the conduct of DoD-related human subjects research but is not an authoritative list of all regulations or guidance that may apply to such research. Check with your DoD component for more information.